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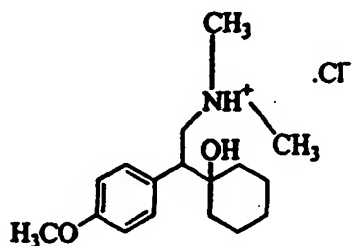
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(54) Title: NOVEL CRYSTALLINE POLYMORPHIC FORMS OF VENLAFAXINE HYDROCHLORIDE AND A PROCESS FOR THEIR PREPARATION



(I)

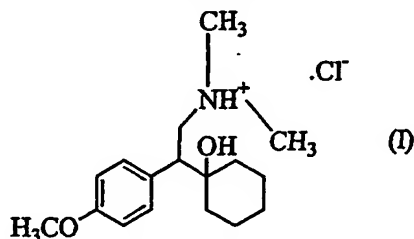
(57) Abstract: The present invention relates to novel crystalline polymorphic forms of Venlafaxine hydrochloride and a process for their preparation. The present invention relates to two polymorphic forms of Venlafaxine hydrochloride. Venlafaxine hydrochloride, N,N-dimethyl-2-(1-hydroxycyclohex-1-yl)-2-(4-methoxyphenyl)ethyl amine hydrochloride, has the formula (I) given below.

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NOVEL CRYSTALLINE POLYMORPHIC FORMS OF VENLAFAXINE HYDROCHLORIDE AND A PROCESS FOR THEIR PREPARATION

Field of the Invention

The present invention relates to novel crystalline polymorphic Forms of Venlafaxine hydrochloride and a process for their preparation. The present invention relates to two polymorphic Forms of Venlafaxine hydrochloride. Venlafaxine hydrochloride, N, N-dimethyl-2-(1-hydroxycyclohex-1-yl)-2-(4-methoxy phenyl)ethyl amine hydrochloride, has the formula (I) given below:



During the microscopic examination to choose a single crystal suitable for X-ray diffraction studies, we found two types of crystals differing in their morphology. This prompted us into further investigation of the possibility of polymorphism in Venlafaxine hydrochloride. It is interesting to note that Venlafaxine hydrochloride, being flexible molecule, is a putative candidate for conformational polymorphism. Venlafaxine facilitates neurotransmission in the brain by blocking both presynaptic reuptake of serotonin and noradrenaline. Venlafaxine exists as a racemic mixture. The (-) enantiomer and the (+) enantiomer inhibits, respectively, reuptake of noradrenaline and serotonin. It antagonizes reserpine-induced hyperthermia. It differs from that of tricyclic antidepressant drugs as it has no significant affinity for adrenergic, muscarinic cholinergic or histamine H receptors. It does not significantly affect cardiac conditions. Venlafaxine is presented as its hydrochloride in tablet form. The Forms 1, 2 and mixture of Form 1 and 2 of Venlafaxine hydrochloride are also useful as antidepressant drug.

Background of Invention

Polymorphism is very common among pharmaceutical substances. It is commonly defined as the ability of any substance to exist in two or more crystalline phases that in the packing arrangement and / or conformation of the molecules in the crystal
5 lattice. Quite often drug substances encapsulate solvent molecules when crystallized. These solvates / hydrates are referred to as pseudopolymorphs. Occasionally even amorphous forms are also encountered. Different polymorphs / pseudopolymorphs differ in their physical properties such as melting point, solubility, chemical reactivity etc. These can appreciably influence pharmaceutical properties such as
10 dissolution rate and bioavailability. It is therefore important to evaluate the polymorphism of drug substances. Rantidine, Sulfathiazole, Indomethacin etc., are some of the important examples of pharmaceuticals that exhibit polymorphism.

A series of 2- phenyl-2-(1-hydroxycycloalkyl)ethylamine derivatives were prepared
15 by G. E. Morris Husbands et al of American home products and were examined for antidepressant activity. Neurotransmitter uptake inhibition was highest for 2- phenyl-2- (1-hydroxycyclohexyl) ethylamine group of compounds in which the aryl ring has a halogen or methoxy substitution at the 3- and / or 4- positions, particularly 1-(1-(3,4-dichlorophenyl)-2-(dimethylamino)ethyl) cyclohexanol and 1-(2-
20 (dimethylamino)-1-(4-methoxy phenyl)ethyl)cyclohexanol (venlafaxine) showed acute and rapid onset of antidepressant activity.

It has now been found that Venlafaxine hydrochloride can exist in any of the several novel crystalline forms, polymorphic forms that differ from each other in their
25 stability, physical properties, spectral data and methods of preparation. Two polymorphs of these novel polymorphic forms and their mixture, that are prepared and characterized, during our research work, are described in this application and are referred to as Form 1, 2 and mixture of Form 1 and 2.

Brief Description of the Invention

The present invention provides three novel polymorphic forms of Venlafaxine hydrochloride. The present invention also provides a process for preparing the three novel polymorphic Forms namely Form 1, 2 and mixture of Form 1 and 2.

5

A saturated solution of Venlafaxine hydrochloride in dioxane at reflux temperature on cooling gives Form 1 of Venlafaxine hydrochloride. On the other hand, recrystallization of Venlafaxine hydrochloride from a mixture of ethyl acetate and methanol at subambient temperature yields Form 2. Recrystallization of Venlafaxine hydrochloride from medium polar solvents at reflux temperature or from a mixture of polar solvents and medium polar solvents yields a mixture of Form 1 and 2.

10

All these polymorphic Forms were proved to be identical in solution as evident from Nuclear Magnetic Resonance (NMR) and Mass Spectral Data. On the other hand, solid state techniques like Infrared (IR) spectroscopy, Differential Scanning Calorimetry (DSC) & Powder X-ray diffractometry (XRD) revealed the difference among these Forms:

15

The present invention provides three novel crystalline polymorphic Forms of Venlafaxine hydrochloride, which are characterized by differential scanning calorimetry. The thermal characteristics of the Forms are presented in Table 1. The DSC thermograms of the Forms are depicted in figures 1, 2 and 3. Multiplot of DSC thermograms of these Forms are shown in figure 4.

20

Table 1. The thermal events (exotherms or endotherms) and the relevant temperatures

Form	Thermal Events 1, 2	Fig. No.
Form - 1	211↓, 245↓(dec.)	1
Form - 2	221↓, 255↓(dec.)	2

25

Mixture of Form 1 and 2	211↓, 219↓, 251↓(dec.)	3
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1↓ - endotherm;

2↓(dec.) - endothermic decomposition

- 5 The present invention provides three novel crystalline polymorphic Forms of Venlafaxine hydrochloride, which are further characterized by infrared spectrum in potassium bromide pellet. The characteristic absorption bands (cm^{-1}) of the Forms are listed in Table 2. The infrared spectra of the Forms are depicted in figures 5 - 7.

Table-2. The FT-IR absorption maxima (cm^{-1})

Form -1(Fig. 5)	Form - 2 (Fig. 6)	Mixture of Form 1&2 (Fig. 7)
3365		
	3352	3353
3324		3326
	3016	3016
3003		
2944		2943
2936	2936	
	2857	2856
2851		2851
	2835	2832
2674		
2587	2583	2585
2522		2519
	2515	
2484		2483
	2480	
1612	1614	1613

1583	1582	1583
1513	1514	1513
1474	1473	1473
1442	1439	1441
1404	1401	1403
1388	1385	1387
1366	1367	1366
1303	1307	1303
1275	1275	1275
1243	1247	1246
1180	1179	1179
	1169	
1153	1153	1153
1141	1141	1141
1108	1110	1109
1081	1083	1081
1061	1062	1062
	1043	1040
1039	1035	
981	982	
970	972	971
959	957	958
928	929	929
909	909	909
	837	
830		831
818		818
	811	
	778	
770	768	769

	740	
735		736
594		592
	581	
	553	
547		
528		
	523	525

The present invention provides three novel crystalline polymorphic Forms of Venlafaxine hydrochloride, which are further characterized by powder X-ray diffraction. The characteristic powder diffraction peaks are expressed in degrees 2 θ . The positions of the peaks (2 θ) for all the Forms are presented in Table 3. The powder X-ray diffractograms of these Forms are depicted in figures 8-10. Multiplot of X-ray diffractograms of these Forms are shown in figure 11.

Table-3. The position (2-theta) of intense peaks.

FORM-1 (Fig.8)	FORM-2 (Fig.9)	Mixture of Form 1 & 2 (Fig.10)
6.74		6.72
	6.84	
	8.44	8.34
10.26	10.30	10.20
	12.80	12.68
13.50		13.50
	13.62	
15.06		15.00
15.48		15.42
	15.66	
	16.06	15.94
	16.40	16.32

16.48		
		16.80
16.90	16.88	16.90
17.30		17.32
	17.44	
18.24		18.20
	18.52	
	19.04	18.94
19.76		19.74
	19.84	
20.30		20.30
	20.48	
21.20		21.18
	21.30	
21.70		21.68
	21.88	
22.70		22.68
23.98		
	25.14	25.04
25.30		25.36
25.60		25.60
	25.80	
	26.24	26.26
	26.38	
26.56		
	26.98	
27.18		27.16
	27.40	27.28
27.58		27.58
		28.04
28.20		28.18

	28.62	28.52
28.74		
	28.96	28.86
29.28		29.26
29.74		
	31.08	
31.22	31.24	31.16
31.54		31.56
	31.82	
31.98		32.04
32.20		
		32.42
32.80	32.84	32.76
33.08		33.00
	33.34	33.24
	34.06	33.96
34.16		34.16
35.06		35.06
	35.28	
37.60		37.50
	38.76	38.66
	39.28	
	41.56	
41.78		
42.06		42.02

The present invention provides two polymorphs of Venlafaxine hydrochloride that are further characterized by the crystal parameters obtained from the single crystal X-ray diffraction analysis. The crystal parameters for Form 1 and Form 2 are

5 presented in Table 4.

Table 4. Crystal data

	Form 1	Form 2
Unit cell dimensions: a	26.191(2)	5.797(6)
b	5.875(2)	26.074(7)
c	11.430(1)	11.722(3)
α	90.00	90.0
β	90.00	100.72(5)
γ	90.00	90.0
Unit cell volume: V	1758.7(0.6)	1740.9(2.0)
Crystal System	Orthorhombic	Monoclinic
Space Group	Pca2 ₁	P2 ₁ /n
Density, g/cc	1.18	1.20

The invention also provides polymorphs of Venlafaxine hydrochloride that are further characterized by the atomic positions and other structural parameters obtained from the single crystal X-ray diffraction analysis. The results of X-ray structure determination of Form - 1 and Form - 2 are given in Tables 5 and 6 respectively. The bond distances and bond angles of the two Forms are compared in Table 7 and 8 respectively. The molecular structure for Form 1 and Form 2 are depicted in figure 12 and 13 respectively.

10

Table 5: Atomic position and Isotropic Displacement parameters – Form 1

Atom	X	Y	Z	B (eq)
Cl(1)	0.52086(4)	0.3390(1)	0.6274	4.95(2)
O(1)	0.38450(8)	0.5010(3)	0.2815(2)	3.68(5)
O(2)	0.3219(1)	0.0516(4)	0.7996(2)	5.10(6)
N(1)	0.49072(9)	-0.0332(5)	0.3415(3)	3.88(6)
C(1)	0.3685(1)	0.2701(5)	0.2553(3)	3.15(6)
C(2)	0.3113(1)	0.2653(6)	0.2784(3)	4.30(8)

C(3)	0.2818(1)	0.4149(7)	0.1948(4)	5.1(1)
C(4)	0.2919(2)	0.3608(8)	0.0685(4)	6.0(1)
C(5)	0.3488(1)	0.3680(7)	0.0427(3)	5.03(9)
C(6)	0.3783(1)	0.2167(5)	0.1258(3)	4.03(7)
C(7)	0.3982(1)	0.1021(5)	0.3352(3)	3.26(6)
C(8)	0.4546(1)	0.1659(5)	0.3363(3)	3.42(6)
C(9)	0.4837(1)	-0.1783(6)	0.4477(3)	4.92(9)
C(10)	0.5447(1)	0.0519(7)	0.3353(4)	5.30(9)
C(11)	0.3767(1)	0.0885(5)	0.4582(3)	3.30(6)
C(12)	0.3824(1)	0.2614(6)	0.5396(3)	3.73(7)
C(13)	0.3638(1)	0.2461(6)	0.6502(3)	4.03(8)
C(14)	0.3375(1)	0.0498(6)	0.6853(3)	3.93(8)
C(15)	0.3300(1)	-0.1216(5)	0.6065(3)	4.17(8)
C(16)	0.3494(1)	-0.1012(6)	0.4941(3)	3.75(7)
C(17)	0.3033(2)	-0.1535(7)	0.8472(4)	6.1(1)
H(1)	0.3055	0.2922	0.3568	2.7518
H(2)	0.2991	0.0925	0.2775	4.3532
H(3)	0.2516	0.4127	0.2165	5.1071
H(4)	0.2921	0.5942	0.2082	6.2537
H(5)	0.2709	0.4537	0.0170	6.2373
H(6)	0.2825	0.1945	0.0510	5.1947
H(7)	0.3555	0.3047	-0.0362	4.1152
H(8)	0.3606	0.5216	0.0555	4.9694
H(9)	0.4146	0.2188	0.1072	3.7679
H(10)	0.3687	0.0493	0.1165	6.2898
H(11)	0.3921	-0.0490	0.2952	2.4811
H(12)	0.4642	0.2380	0.2685	3.1954
H(13)	0.4654	0.2653	0.4014	3.7616
H(14)	0.4488	-0.2478	0.4444	5.8938
H(15)	0.4893	-0.0876	0.5276	5.4603
H(16)	0.5121	-0.2952	0.4545	6.4714

H(17)	0.5479	0.1476	0.2569	6.8441
H(18)	0.5655	-0.0704	0.3235	6.3483
H(19)	0.5499	0.1674	0.4194	9.6737
H(20)	0.4003	0.4150	0.5127	5.9622
H(21)	0.3708	0.3692	0.7136	4.0175
H(22)	0.3147	-0.2582	0.6295	4.8832
H(23)	0.3457	-0.2144	0.4514	2.6635
H(24)	0.3313	-0.2652	0.8383	8.3926
H(25)	0.2971	-0.1385	0.9355	8.6633
H(26)	0.2720	-0.1827	0.8053	9.0576
H(27)	0.4067	0.5201	0.2424	11.8903
H(28)	0.4834	-0.1273	0.2640	8.3028

Table 6: Atomic position and Isotropic Displacement parameters – Form 2

Atom	X	Y	Z	B (eq)
Cl(1)	0.1136(2)	0.27713(5)	0.74321(9)	4.92
O(1)	-0.1465(5)	0.1315(1)	0.4067(2)	4.09(7)
O(2)	0.5104(6)	0.0643(1)	0.9167(2)	5.31(8)
N(1)	0.3859(6)	0.2440(1)	0.4521(3)	3.92(8)
C(1)	0.0830(7)	0.1177(1)	0.3844(3)	3.50(9)
C(2)	0.1117(9)	0.0602(2)	0.4086(3)	4.6(1)
C(3)	-0.062(1)	0.0280(2)	0.3259(4)	5.8(1)
C(4)	-0.053(1)	0.0390(2)	0.2000(4)	6.1(1)
C(5)	-0.0829(9)	0.0959(2)	0.1748(3)	4.8(1)
C(6)	0.0934(8)	0.1276(1)	0.2567(3)	3.96(9)
C(7)	0.2705(7)	0.1502(1)	0.4644(3)	3.37(9)
C(8)	0.1927(7)	0.2064(1)	0.4590(3)	3.54(9)
C(9)	0.5792(9)	0.2421(2)	0.5556(5)	5.8(1)
C(10)	0.284(1)	0.2965(2)	0.4331(5)	6.1(1)
C(11)	0.3330(7)	0.1295(1)	0.5874(3)	3.50(9)

C(12)	0.1869(8)	0.1364(2)	0.6675(3)	4.1(1)
C(13)	0.2418(8)	0.1154(2)	0.7779(3)	4.2(1)
C(14)	0.4408(8)	0.0872(2)	0.8105(3)	4.0(1)
C(15)	0.5923(8)	0.0804(2)	0.7321(4)	4.6(1)
C(16)	0.5392(8)	0.1015(2)	0.6228(3)	4.3(1)
C(17)	0.359(1)	0.0703(2)	0.9984(4)	5.7(1)
H(1)	0.1204	0.0521	0.4917	6.7680
H(2)	0.2866	0.0438	0.4173	9.7144
H(3)	-0.0204	-0.0098	0.3445	7.0356
H(4)	-0.2155	0.0366	0.3410	6.8771
H(5)	0.1044	0.0257	0.2046	7.2092
H(6)	-0.1748	0.0209	0.1361	7.5569
H(7)	-0.0791	0.1025	0.0958	3.0118
H(8)	-0.2571	0.1071	0.1720	5.2585
H(9)	0.0526	0.1675	0.2365	5.1392
H(10)	0.2363	0.1171	0.2520	4.6880
H(11)	0.4034	0.1485	0.4331	4.4638
H(12)	0.0736	0.2159	0.3880	2.9114
H(13)	0.1484	0.2158	0.5391	4.6824
H(14)	0.6871	0.2744	0.5504	5.0745
H(15)	0.5174	0.2468	0.6264	8.4947
H(16)	0.6513	0.2045	0.5634	4.7042
H(17)	0.2310	0.3081	0.4974	9.0568
H(18)	0.1414	0.2969	0.3547	9.7398
H(19)	0.4101	0.3192	0.4233	8.1898
H(20)	0.0505	0.1543	0.6478	2.8021
H(21)	0.1491	0.1238	0.8369	5.1493
H(22)	0.7205	0.0631	0.7581	3.5305
H(23)	0.6379	0.0931	0.5665	4.9938
H(24)	0.1977	0.0623	0.9626	5.2548
H(25)	0.3497	0.1104	1.0175	6.6356

H(26)	0.4285	0.0552	1.0713	4.9450
H(27)	-0.2297	0.1535	0.3442	5.3067
H(28)	0.4293	0.2387	0.3858	6.7097

Table -7: Comparison of Bond distances of Form 1 and Form 2

Atom	Atom	Form 1	Form 2	Atom	Atom	Form 1	Form 2
O1	C1	1.451(4)	1.449(5)	C4	C5	1.521(6)	1.517(6)
O2	C14	1.369(4)	1.371(5)	C5	C6	1.512(5)	1.511(6)
O2	C17	1.410(4)	1.422(5)	C7	C8	1.524(4)	1.532(5)
N1	C8	1.506(4)	1.501(5)	C7	C11	1.515(4)	1.519(5)
N1	C9	1.495(5)	1.491(6)	C11	C12	1.386(4)	1.388(5)
N1	C10	1.500(4)	1.491(6)	C11	C16	1.386(4)	1.396(5)
C1	C2	1.523(4)	1.528(5)	C12	C13	1.358(4)	1.387(5)
C1	C6	1.534(4)	1.531(5)	C13	C14	1.401(5)	1.362(6)
C1	C7	1.553(4)	1.549(6)	C14	C15	1.366(5)	1.395(6)
C2	C3	1.510(5)	1.516(6)	C15	C16	1.387(4)	1.376(5)
C3	C4	1.501(6)	1.515(6)				

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parenthesis.

Table - 8: Comparison of Bond angles of Form 1 and Form 2

Atom	Atom	Atom	Form 1	Form 2	Atom	Atom	Atom	Form 1	Form 2
C14	O2	C17	117.7(3)	116.8(4)	C1	C7	C8	109.4(2)	109.3(3)
C8	N1	C9	113.4(2)	113.0(3)	C1	C7	C11	113.2(2)	113.4(3)
C8	N1	C10	109.3(2)	109.3(3)	C8	C7	C11	111.4(2)	113.3(3)
C9	N1	C10	110.1(3)	111.6(4)	N1	C8	C7	114.8(2)	114.2(3)
O1	C1	C2	105.4(3)	106.4(3)	C7	C11	C12	122.9(2)	121.9(4)
O1	C1	C6	110.0(2)	109.9(3)	C7	C11	C16	120.6(3)	120.5(3)
O1	C1	C7	109.2(2)	108.6(3)	C12	C11	C16	116.5(3)	117.6(3)
C2	C1	C6	109.1(2)	108.9(3)	C11	C12	C13	122.5(3)	121.1(4)

C2	C1	C7	112.2(3)	112.6(3)	C12	C13	C14	119.9(3)	120.7(4)
C6	C1	C7	110.8(2)	110.5(3)	O2	C14	C13	114.4(3)	125.4(4)
C1	C2	C3	112.5(3)	112.9(4)	O2	C14	C15	126.3(3)	115.4(4)
C2	C3	C4	113.3(3)	112.2(4)	C13	C14	C15	119.2(3)	119.2(4)
C3	C4	C5	110.6(3)	110.6(4)	C14	C15	C16	119.6(3)	120.3(4)
C4	C5	C6	111.3(3)	111.8(3)	C11	C16	C15	122.2(3)	121.1(4)
C1	C6	C5	113.6(3)	112.6(3)					

Angles are in degrees. Estimated standard deviations in the least significant figure given in parentheses.

5

Table 9. Comparison of Selected torsion angles

Atom	Atom	Atom	Atom	Form 1	Form 2
N1	C8	C7	C1	-143.9(3)	-137.5(3)
N1	C8	C7	C11	90.2(3)	94.9(4)
C1	C7	C11	C12	-72.6(3)	-76.9(5)
C8	C7	C11	C12	51.3(4)	48.5(5)
C1	C7	C11	C16	106.7(3)	101.5(4)
C8	C7	C11	C16	-129.5(3)	-133.2(4)

Angles are in degrees. Estimated standard deviations in the least significant figure given in parentheses.

10

The DSC thermogram of Form 1 has characteristic melting endotherm at 211 °C (Fig. 1) with an onset temperature at 208 °C followed by a decomposition endotherm at 245 °C.

15

Form 2 has a characteristic melting endotherm at 221 °C (Fig. 2) with an onset temperature at 216 °C followed by a decomposition endotherm at 255 °C.

The mixture of Form 1 and 2 has two endotherms at 211 °C and 219 °C (Fig. 3) which are due to the melting of Form 1 and 2 respectively. The endotherm at 251 °C corresponds to the decomposition of the compound.

The characteristic infrared spectra (Figs. 5 - 7) of these Forms differ from one another. A qualitative comparison of the spectral data at different regions reveals the following differences.

Form 1 exhibits absorption at 3365 and 3324 cm^{-1} , while Form 2 has only broad absorption at 3352 cm^{-1} (Fig. 14).

Form 1 has a peak at 3003 cm^{-1} while in Form 2, it is at 3016 cm^{-1} (Fig. 14).

Form 1 absorbs at 2944 and 2923 cm^{-1} while Form 2 absorbs only at 2936 cm^{-1} (Fig. 14).

Form 1 displays peaks at 2675, 2587, 2522 and 2484 cm^{-1} while Form 2 has peaks at 2583, 2516, 2480 cm^{-1} (Fig. 14).

Peak at 1180 cm^{-1} in Form 1 splits as 1179 and 1169 cm^{-1} in Form 2 (Fig. 15).

Peak at 1039 cm^{-1} in Form 1 splits as 1043 and 1035 cm^{-1} in Form 2 (Fig. 15).

Form 1 shows peaks at 830 and 818 cm^{-1} while Form 2 has peaks at 837 and 811 cm^{-1} respectively (Fig. 16).

Form 1 shows two peaks at 770 and 735 cm^{-1} while Form 2 has three peaks at 778, 768 and 740 cm^{-1} respectively (Fig. 16).

Form 1 shows peaks at 594, 547 and 528 cm^{-1} while Form 2 has peaks at 581, 553 and 523 cm^{-1} respectively (Fig. 16).

The powder X-ray diffractograms of the crystalline polymorphic Forms 1, 2 and the mixture of Form 1 and 2 were found to be different from each other (Fig. 11 and Table 3).

The single crystal X-ray diffraction studies of Forms 1 and 2 clearly demonstrate the difference in their crystal structures as evidenced by their different unit cell dimensions and space groups (Table 4). The molecular structures of Form 1 (Fig. 12) and Form 2 (Fig. 13) differ from each other in their rotational

conformation. This is clear from the comparison of the torsion angles presented in Table 9. Hence Forms 1 and 2 are conformational polymorphs. As shown in Table 4, the calculated density (g/cc) for the Form 1 and Form 2 are 1.18 and 1.20 respectively. This results supports Form 2 as the thermodynamically stable form at room temperature since the most dense crystal at a given temperature is considered to be the most thermodynamically stable (cf. J. Halebian and W. McCrone, J. Pharm. Sci., 58(8), 911 (1969)). Further Form 2 has higher melting point than Form 1.

The results of a single crystal X-ray analysis are limited to, as the name implies, the sole crystal placed in the X-ray beam. On the other hand, the results from powder diffraction represents the contribution from many crystalline particles in the sample exposed to X-rays. Powder X-ray diffraction pattern can be computed from the results of single crystal analysis. This pattern can be compared with the experimental powder X-ray pattern. Comparison of the calculated and experimental diffraction patterns will confirm if the results of the two techniques are the same. The computed powder X-ray diffraction patterns of the Form 1 and Form 2 of Venlafaxine hydrochloride are displayed in figure 17 and 18 respectively. These calculated pattern match reasonably well with their respective experimental pattern viz., figures 8 and 9. The primary powder X-ray diffraction pattern provides an unambiguous description of each of two polymorphs of Venlafaxine hydrochloride.

Detailed Description of the Invention

According to a feature of the present invention there is provided a novel polymorphic Form-1 of Venlafaxine hydrochloride of the formula (I) having the following characteristic data.

Differential Scanning Calorimeter : Endotherms at 211 °C and 245 °C (dec.) (Fig. 1)

Infrared absorption bands (cm^{-1}): 3365, 3324, 3003, 2944, 2936, 2851, 2674, 2587, 2522, 2484, 1612, 1583, 1513, 1474, 1442, 1404, 1388, 1366, 1303, 1275, 1243,

1180, 1153, 1141, 1108, 1081, 1061, 1039, 981, 970, 959, 928, 909, 830, 818, 770, 735, 594, 547, 528 (Fig. 5)

X-ray powder diffraction peaks (2θ): 6.74, 10.26, 13.50, 15.06, 15.48, 16.48, 16.90, 17.30, 18.24, 19.76, 20.30, 21.20, 21.70, 22.70, 23.98, 25.30, 25.60, 26.56, 27.18, 27.58, 28.20, 28.74, 29.28, 29.74, 31.22, 31.54, 31.98, 32.20, 32.80, 33.08, 34.16, 35.06, 37.60, 41.78, 42.06 (Fig. 8)

According to another feature of the present invention there is provided a novel polymorphic Form-2 of Venlafaxine hydrochloride of the formula (I) having the following characteristic data.

Differential Scanning Calorimeter : Endotherms at 221 °C, 255 °C (dec.) (Fig. 2)

Infrared absorption bands (cm^{-1}): 3352, 3016, 2936, 2857, 2835, 2583, 2515, 2480, 1614, 1582, 1514, 1473, 1439, 1401, 1385, 1367, 1307, 1275, 1247, 1179, 1169, 1153, 1141, 1110, 1083, 1062, 1043, 1035, 982, 972, 957, 929, 909, 837, 811, 778, 768, 740, 581, 553, 523 (Fig. 6)

X-ray powder diffraction peaks (2θ): 6.84, 8.44, 10.30, 12.80, 13.62, 15.66, 16.06, 16.40, 16.88, 17.44, 18.52, 19.04, 19.84, 20.48, 21.30, 21.88, 25.14, 25.80, 26.24, 26.38, 26.98, 27.40, 28.62, 28.96, 31.08, 31.24, 31.82, 32.84, 33.34, 34.06, 35.28, 38.76, 39.28, 41.56 (Fig. 9)

20

According to another feature of the present invention there is provided a mixture of novel polymorphic Forms 1 and 2 of Venlafaxine hydrochloride of the formula (I) having the following characteristic data.

Differential Scanning Calorimeter: Endotherms at 211 °C, 219 °C and 251 °C (dec.) (Fig. 3).

25

Infrared absorption bands (cm^{-1}): 3353, 3326, 3016, 2943, 2856, 2851, 2832, 2585, 2519, 2483, 1613, 1583, 1513, 1473, 1441, 1403, 1387, 1366, 1303, 1275, 1246, 1179, 1153, 1141, 1109, 1081, 1062, 1040, 971, 958, 929, 909, 831, 818, 769, 736, 592, 525 (Fig. 7)

X-ray powder diffraction peaks (2 θ): 6.72, 8.34, 10.20, 12.68, 13.50, 15.00, 15.42, 15.94, 16.32, 16.80, 16.90, 17.32, 18.20, 18.94, 19.74, 20.30, 21.18, 21.68, 22.68, 25.04, 25.36, 25.60, 26.26, 27.16, 27.28, 27.58, 28.04, 28.18, 28.52, 28.86, 29.26, 31.16, 31.56, 32.04, 32.42, 32.76, 33.00, 33.24, 33.96, 34.16, 35.06, 37.50, 38.66, 42.02 (Fig. 10)

According to another embodiment of the present invention there is provided a process for the preparation of novel polymorphic Form-1 of Venlafaxine hydrochloride of the formula I, having the characteristics described earlier, which comprises:

- (i) synthesizing Venlafaxine hydrochloride by employing known methods,
- (ii) dissolving the compound obtained in step (i) in a medium polar or polar organic solvent at the reflux temperature,
- (iii) filtering the resulting solution and cooling to room temperature slowly for a period in the range of 1 to 8 hrs and stirring the reaction mixture for 20 to 36 hrs,
- (iv) filtering to produce the polymorphic Form-1 of Venlafaxine hydrochloride.

The medium polar or polar organic solvents are selected from 1,4-dioxane, 1,3-dioxane, and tetrahydrofuran and isopropanol.

The cooling in step (iii) is effected by allowing the solution to attain room temperature on its own or with mild coolants like cold water / water at room temperature.

According to another embodiment of the present invention, there is provided a process for the preparation of novel polymorphic Form-2 of Venlafaxine hydrochloride of the formula I, having the characteristics described earlier, which comprises:

- (i) synthesizing Venlafaxine hydrochloride by employing known methods,

- (ii) dissolving the compound obtained in step (i) in an organic polar solvent and adding an organic solvent of medium polarity at 0 to 10° C,
- (iii) maintaining the resulting solution slowly to a temperature in the range of 0 to 10° C over a period in the range of 12 to 24 hrs and
- 5 (iv) filtering to produce the polymorphic Form-2 of Venlafaxine hydrochloride.

The cooling in step (iii) is effected using ice, ice-salt mixture, dry ice and liquid nitrogen.

- 10 According to another feature of the present invention, there is provided a process for the preparation of mixture of Form 1 and Form 2 of Venlafaxine hydrochloride of the formula I, having the characteristics described earlier, which comprises:

- (i) synthesizing Venlafaxine hydrochloride by employing known methods,
- 15 (ii) dissolving the compound obtained in step (i) in an organic polar solvent at room temperature,
- (iii) adding medium polar organic solvent until the turbidity appears and allowing the solution to precipitate at an ambient temperature for a period in the range of 12-36 hr and
- 20 (iv) filtering and drying to obtain the mixture of Form 1 and 2 of Venlafaxine hydrochloride.

The organic polar solvents are selected from methanol, ethanol and isopropanol. The medium polar organic solvent employed are selected from
25 acetonitrile, methyl isobutyl ketone, ethylacetate, n-butyl acetate and diisopropyl ether.

According to another feature of the present invention, there is provided an alternate process for the preparation of mixture of Form 1 and Form 2 of Venlafaxine

hydrochloride of the formula I, having the characteristics described earlier, which comprises:

- (i) synthesizing Venlafaxine hydrochloride by employing known methods,
- (ii) heating the compound in an organic solvent and cooling the resulting clear
5 solution and
- (iii) filtering and drying to obtain the mixture of Form 1 and 2 of Venlafaxine hydrochloride.

The organic solvents are selected from isopropanol, acetonitrile, methyl
10 isobutyl ketone, ethylacetate, n-butyl acetate and diisopropyl ether.

The cooling in step (iii) is effected using ice, ice-salt mixture, dry ice and liquid nitrogen.

The present invention provides a pharmaceutical composition, containing the
15 polymorphic forms of Venlafaxine hydrochloride the formula (I) as defined above, in combination with the usual pharmaceutically employed carriers, diluents and the like, useful for the treatment and / or prophylaxis of depression, anxiety, neuropathy.

The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like, may
20 contain flavourants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 1 to 25 %, preferably 1 to 15 % by weight of active ingredient, the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents.

25 The polymorphic forms of the formula (I) as defined above are clinically administered to mammals, including man, via either oral, nasal, pulmonary, transdermal or parenteral, rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and
30 irritation of injection. However, in circumstances where the patient cannot swallow

the medication, or absorption following oral administration is impaired, as by disease or other abnormality, it is essential that the drug be administered parenterally. By either route, the dosage is in the range of about 0.01 to about 100 mg / kg body weight of the subject per day or preferably about 0.01 to about 30 mg / kg body weight per day administered singly or as a divided dose. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for treatment, generally smaller doses being administered initially and thereafter increments made to determine the most suitable dosage.

Suitable pharmaceutically acceptable carriers include solid fillers or diluents and sterile aqueous or organic solutions. The active ingredient will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage in the range as described above. Thus, for oral administration, the polymorphic form can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavourants, sweeteners, excipients and the like. For parenteral administration, the polymorphic form can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds. Aqueous solutions with the active ingredient dissolved in polyhydroxylated castor oil may also be used for injectable solutions. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

For nasal administration, the preparation may contain the polymorphic forms of the present invention dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, such as propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin or preservatives such as parabenes.

Tablets, dragees or capsules having talc and / or a carbohydrate carried binder or the like are particularly suitable for any oral application. Preferably, carriers for tablets, dragees or capsules include lactose, corn starch and / or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet production method is exemplified below :

Tablet Production Example :

a) 1) Active ingredient	30 g
2) Lactose	95 g
10 3) Corn starch	30 g
4) Carboxymethyl cellulose	44 g
5) Magnesium stearate	1 g
<hr/>	
200 g for 1000 tablets	

15 The ingredients 1 to 3 are uniformly blended with water and granulated after drying under reduced pressure. The ingredient 4 and 5 are mixed well with the granules and compressed by a tableting machine to prepare 1000 tablets each containing 30 mg of active ingredient.

20 b) 1) Active ingredient	30 g
2) Calcium phosphate	90 g
3) Lactose	40 g
4) Corn starch	35 g
5) Polyvinyl pyrrolidone	3.5 g
25 6) Magnesium stearate	1.5 g
<hr/>	
200 g for 1000 tablets	

The ingredients 1-4 are uniformly moistened with an aqueous solution of 5 and granulated after drying under reduced pressure. Ingredient 6 is added and

granules are compressed by a tableting machine to prepare 1000 tablets containing 30 mg of ingredient 1.

The present invention is described in detail in the examples given below which are provided by way of illustration only and therefore should not be construed
5 to limit the scope of the invention.

Example 1

Process for the preparation of Venlafaxine hydrochloride :

Venlafaxine hydrochloride was synthesized starting from p-methoxy phenyl
10 acetonitrile. Condensation of cyclohexanone with p-methoxy phenyl acetonitrile in presence of butyl lithium produced 2-(4-methoxyphenyl)-2-(1-cyclohexanol)acetonitrile in good yield. Catalytic reduction of 2-(4-methoxyphenyl)-2-(1-cyclohexanol)acetonitrile in presence of Rh.Al₂O₃ yielded 2-(4-methoxyphenyl)-2-(1-cyclohexanol)ethylamine. Then, selective methylation of 2-(4-methoxyphenyl)-2-(1-cyclohexanol)ethylamine in presence of free hydroxyl group by
15 heating under reflux with formaldehyde and formic acid yielded N,N-dimethyl-2-(4-methoxyphenyl)-2-(1-cyclohexanol)ethylamine as a syrupy liquid. Venlafaxine hydrochloride was obtained by treating N,N-dimethyl-2-(4-methoxyphenyl)-2-(1-cyclohexanol)ethylamine with isopropanolic hydrochloride in good yield and purity.

20

Examples 2-5 illustrates the Process for the preparation of polymorphic Form-1 Venlafaxine hydrochloride

Examples 2

Venlafaxine hydrochloride (5 g) obtained in example 1 was heated in 1,4-dioxane
25 (250 ml) at reflux temperature until complete dissolution, the hot solution was filtered and allowed to cool to room temperature slowly during a period of 8 hrs. The reaction mass was stirred for 20 hrs at room temperature and the solid formed was filtered and dried to yield 4.12 g (82.4 % yield) of > 99% pure polymorphic Form-1 of Venlafaxine hydrochloride of the formula (I).

Example 3

Venlafaxine hydrochloride (5 g) obtained in example 1 was dissolved in refluxing 1,4-dioxane (200 ml). The solution was filtered hot to remove the undissolved
5 material and allowed to come to room temperature on its own. The crystalline compound was filtered after 30 hr to yield 4.1 g (82 % yield) of > 99% pure polymorphic Form-1 of Venlafaxine hydrochloride of the formula (I).

Example 4

10 Venlafaxine hydrochloride (7.5 g) obtained in example 1 was added to 1,4-dioxane (200 ml) at its refluxing temperature. After 30 min the solution was filtered and cooled rapidly to room temperature. The compound was filtered after 24 hr and dried to yield 6.2 g (82.6 % yield) of > 99% pure polymorphic Form-1 of Venlafaxine hydrochloride of the formula (I).

15

Example 5

Venlafaxine hydrochloride (5 g) obtained in example 1 was dissolved in isopropanol (200 ml) at refluxing temperature. After 30 min the clear solution was filtered and cooled to room temperature. The compound was filtered after 26 hr of stirring at
20 room temperature. The resultant compound was dried to yield 3.75 g (75 % yield) of pure polymorphic Form-1 of Venlafaxine hydrochloride of the formula (I).

Examples 6-7 illustrates the Process for the preparation of polymorphic Form-2 Venlafaxine hydrochloride

Example 6

25 Venlafaxine hydrochloride obtained in example 1 (5 g) was dissolved in methanol (8 ml) at 0 °C, then ethyl acetate (120 ml) was added and cooled between 0 to 5 °C. The fine needles were filtered after 24 hr and dried to yield 3.92 g (78.4% yield) of >99% pure polymorphic Form-2 of Venlafaxine hydrochloride of the formula (I).

Example 7

To a suspension of Venlafaxine hydrochloride obtained in example 1 (5g) methanol (15 ml) was added to dissolve the compound completely. Methyl isobutyl ketone (50 ml), was added to the reaction mass and the solution was cooled to 0 -5 °C. The crystalline compound was filtered and dried to yield 3.8 g (76 % yield) of >99% pure polymorphic Form-2 of Venlafaxine hydrochloride of the formula (I).

Examples 8-10 illustrates the Process for the preparation of mixture of polymorphic Form 1 and 2 of Venlafaxine hydrochloride:

Example 8

Venlafaxine hydrochloride obtained in example 1 (25 g) was dissolved in methanol (30 ml) between 25 - 30° C, then ethyl acetate was added till turbidity appeared. The solution was allowed to stand for 20 hr. The solid thus precipitated was filtered, washed with ethyl acetate and dried to yield fine crystalline mass of 23.6 g (yield 94.4%) of mixture of polymorphic Form 1 and 2 of Venlafaxine hydrochloride of the formula (I).

Example 9

Venlafaxine hydrochloride obtained in example 1 (20 g) was taken in acetonitrile (200 ml) and heated under reflux for 1 hr. The hot solution was filtered and allowed to room temperature. The compound precipitated after 24 hr was filtered and dried to yield white crystalline mass of 17.4 g (yield 86.8%) of mixture of polymorphic Form 1 and 2 of Venlafaxine hydrochloride of the formula (I).

Example 10

Venlafaxine hydrochloride obtained in example 1 (20 g) was taken in isopropanol (150 ml) and heated under reflux with stirring until the compound dissolved completely. The solution was allowed to cool to room temperature while stirring was

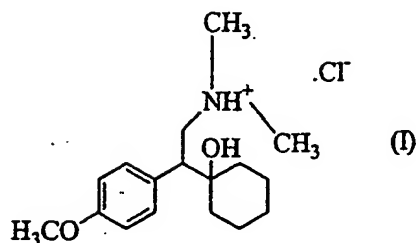
continued. The precipitated compound was filtered and dried to yield white fluffy solid of 16.3 g (81.5%) of mixture of polymorphic Form 1 and 2 of Venlafaxine hydrochloride of the formula (I).

5 Advantages of the invention

- The novel Forms of Venlafaxine hydrochloride are pharmaceutically more acceptable.
- The forms can be easily converted into a formulation resulting in higher activity / bio-availability.
- 10 • Possibility of preparing uniform crystal size of Venlafaxine hydrochloride

We claim

1. Novel polymorphic Form 1 of Venlafaxine hydrochloride having the formula I



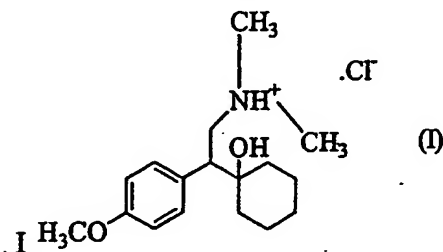
characterized by the following data:

Differential Scanning Calorimeter : Endotherms at 211 °C and 245 °C (dec.),

Infrared absorption bands (cm⁻¹): 3365, 3324, 3003, 2944, 2936, 2851, 2674, 2587, 2522, 2484, 1612, 1583, 1513, 1474, 1442, 1404, 1388, 1366, 1303, 1275, 1243, 1180, 1153, 1141, 1108, 1081, 1061, 1039, 981, 970, 959, 928, 909, 830, 818, 770, 735, 594, 547, 528,

X-ray powder diffraction peaks (2θ): 6.74, 10.26, 13.50, 15.06, 15.48, 16.48, 16.90, 17.30, 18.24, 19.76, 20.30, 21.20, 21.70, 22.70, 23.98, 25.30, 25.60, 26.56, 27.18, 27.58, 28.20, 28.74, 29.28, 29.74, 31.22, 31.54, 31.98, 32.20, 32.80, 33.08, 34.16, 35.06, 37.60, 41.78, 42.06.

2. Novel polymorphic Form 2 of Venlafaxine hydrochloride having the formula



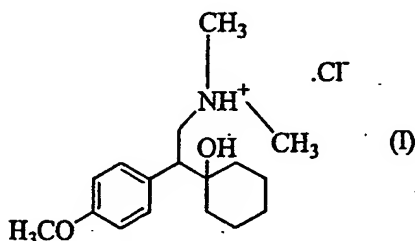
characterized by the following data:

Differential Scanning Calorimeter: Endotherms at 221 °C and 255 °C (dec.),

Infrared absorption bands (cm^{-1}): 3352, 3016, 2936, 2857, 2835, 2583, 2515, 2480, 1614, 1582, 1514, 1473, 1439, 1401, 1385, 1367, 1307, 1275, 1247, 1179, 1169, 1153, 1141, 1110, 1083, 1062, 1043, 1035, 982, 972, 957, 929, 909, 837, 811, 778, 768, 740, 581, 553, 523,

- 5 X-ray powder diffraction peaks (2θ): 6.84, 8.44, 10.30, 12.80, 13.62, 15.66, 16.06, 16.40, 16.88, 17.44, 18.52, 19.04, 19.84, 20.48, 21.30, 21.88, 25.14, 25.80, 26.24, 26.38, 26.98, 27.40, 28.62, 28.96, 31.08, 31.24, 31.82, 32.84, 33.34, 34.06, 35.28, 38.76, 39.28, 41.56.

- 10 3. A mixture of novel polymorphic Form 1 and 2 of Venlafaxine hydrochloride having the formula I:



characterized by the following data:

Differential Scanning Calorimeter : Endotherms at 211 °C, 219 °C and 251 °C
 15 (dec.),

Infrared absorption bands (cm^{-1}): 3353, 3326, 3016, 2943, 2856, 2851, 2832, 2585, 2519, 2483, 1613, 1583, 1513, 1473, 1441, 1403, 1387, 1366, 1303, 1275, 1246, 1179, 1153, 1141, 1109, 1081, 1062, 1040, 971, 958, 929, 909, 831, 818, 769, 736, 592, 525,

- 20 X-ray powder diffraction peaks (2θ): 6.72, 8.34, 10.20, 12.68, 13.50, 15.00, 15.42, 15.94, 16.32, 16.80, 16.90, 17.32, 18.20, 18.94, 19.74, 20.30, 21.18, 21.68, 22.68, 25.04, 25.36, 25.60, 26.26, 27.16, 27.28, 27.58, 28.04, 28.18, 28.52, 28.86, 29.26, 31.16, 31.56, 32.04, 32.42, 32.76, 33.00, 33.24, 33.96, 34.16, 35.06, 37.50, 38.66, 42.02.

4. A process for the preparation of novel polymorphic Form-1 of Venlafaxine hydrochloride having the characteristics defined in claim 1, which comprises:

- (i) synthesizing Venlafaxine hydrochloride by employing known methods,
- (ii) dissolving the compound obtained in step (i) in a medium polar or polar organic solvent at the reflux temperature,
- (iii) filtering the resulting solution and cooling to room temperature slowly for a period in the range of 1 to 8 hrs and stirring the reaction mixture for 20 to 36 hrs,
- (iv) filtering to produce the polymorphic Form-1 of Venlafaxine hydrochloride:

10 5. A process for the preparation of novel polymorphic Form-2 of Venlafaxine

- (i) synthesizing Venlafaxine hydrochloride by employing known methods,
- (ii) dissolving the compound obtained in step (i) in an organic polar solvent and adding an organic solvent of medium polarity at 0 to 10° C,
- (iii) maintaining the resulting solution slowly to a temperature in the range of 0 to 10° C over a period in the range of 12 to 24 hrs and
- (iv) filtering to produce the polymorphic Form-2 of Venlafaxine hydrochloride.

6. A process for the preparation of mixture of novel polymorphic Form 1 and 2 of Venlafaxine hydrochloride having the characteristics defined in claim 3, which comprises:

- (i) synthesizing Venlafaxine hydrochloride by employing known methods,
- (ii) dissolving the compound obtained in step (i) in an organic polar solvent at room temperature,
- (iii) adding medium polar organic solvent until the turbidity appears and allowing the solution to precipitate at an ambient temperature for a period in the range of 12-36 hr and
- (iv) filtering and drying to obtain the mixture of Form 1 and 2 of Venlafaxine hydrochloride.

7. A process for the preparation of mixture of novel polymorphic Form 1 and 2 of Venlafaxine hydrochloride having the characteristics defined in claim 3, which comprises:

- (i) synthesizing Venlafaxine hydrochloride by employing known methods,
- 5 (ii) heating the compound in an organic solvent and cooling the resulting clear solution and
- (iii) filtering and drying to obtain the mixture of Form 1 and 2 of Venlafaxine hydrochloride.

10 8. A process as claimed in claim 4, wherein the medium polar or polar organic solvents are selected from 1,4-dioxane, 1,3-dioxane, tetrahydrofuran or isopropanol.

9. A process as claimed in claims 5 and 6 wherein the organic polar solvents are selected from methanol, ethanol and isopropanol.

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10. A process as claimed in claim 5 and 6, wherein the medium polar organic solvents are selected from acetonitrile, methyl isobutyl ketone, ethylacetate, n-butyl acetate and diisopropyl ether.

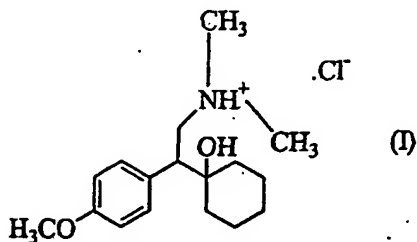
20 11. A process as claimed in claim 7, wherein the organic solvents are selected from isopropanol, acetonitrile, methyl isobutyl ketone, ethylacetate, n-butyl acetate and diisopropyl ether.

12. A process as claimed in claim 4, wherein the cooling is effected using ice, ice-salt mixture, dry ice and liquid nitrogen.

25

13. A process as claimed in claim 5 and 7, wherein the cooling is effected by allowing the solution to attain room temperature on its own or with mild coolants like cold water / water at room temperature.

14. A pharmaceutical composition comprising any one of polymorphic Form selected from Form 1 to 2 or a mixture of polymorphic Form 1 and 2 of Venlafaxine of the formula I



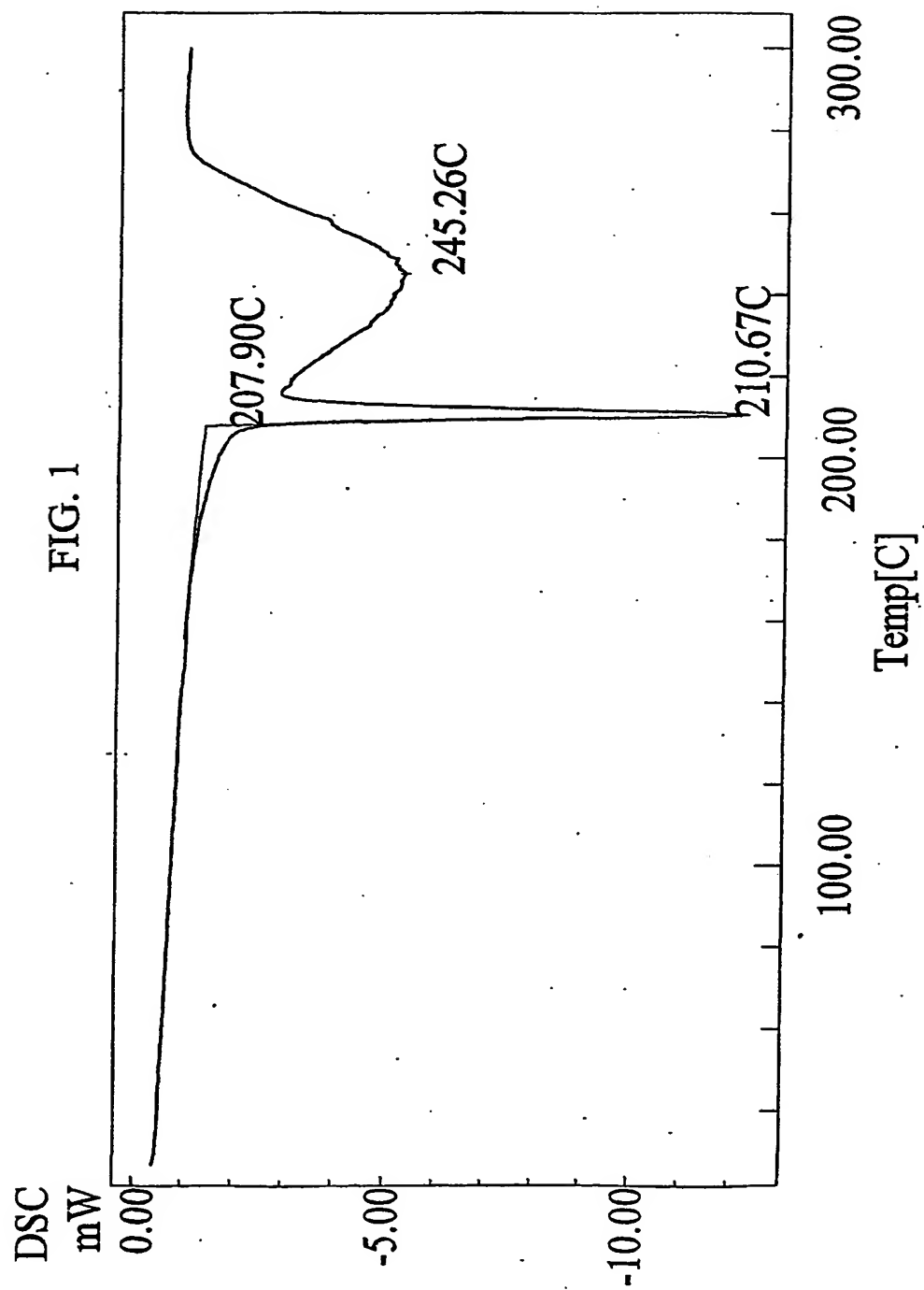
5 and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

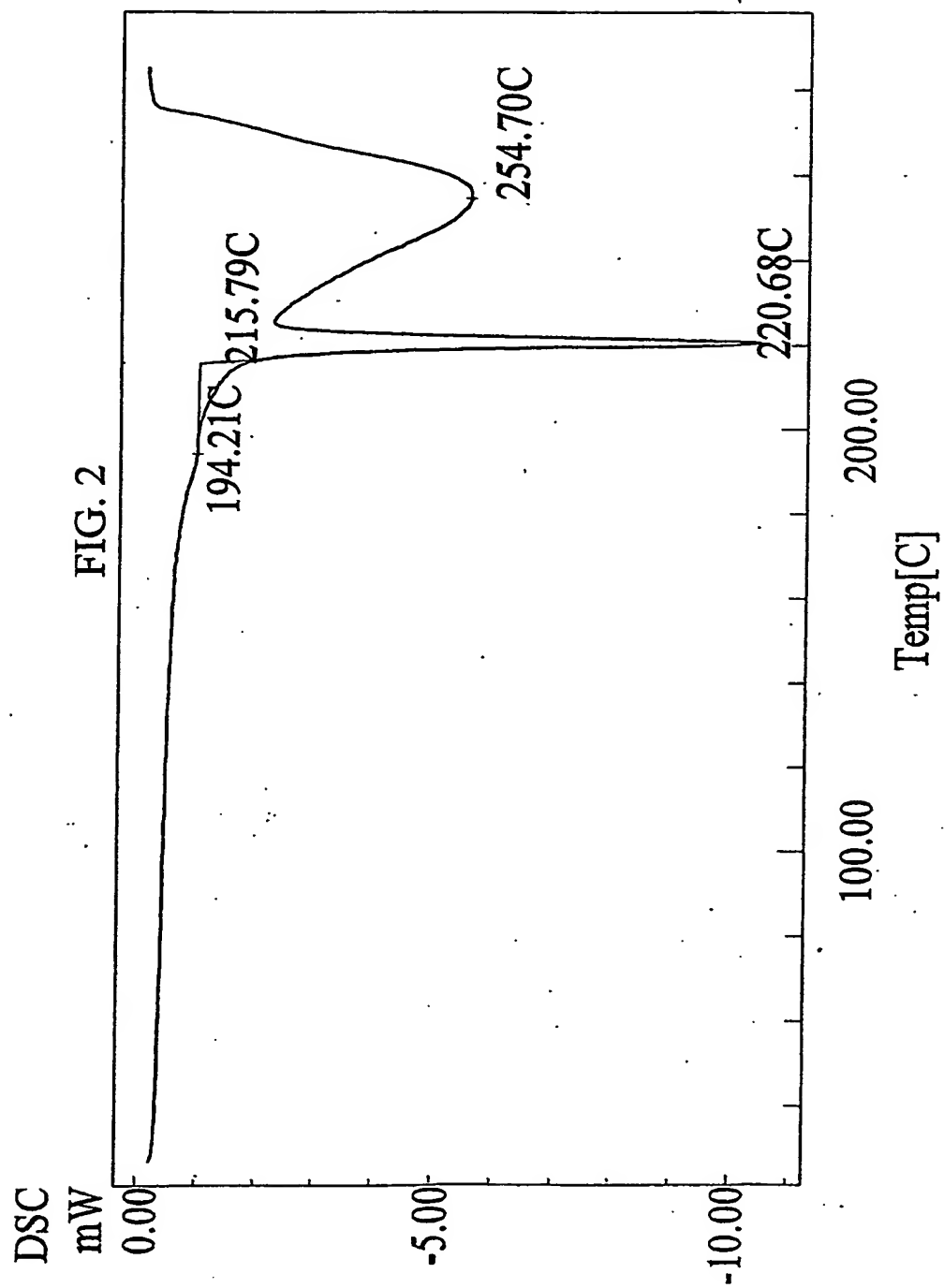
15. A pharmaceutical composition as claimed in claim 14, in the form of a tablet, capsule, powder, syrup, solution or suspension.

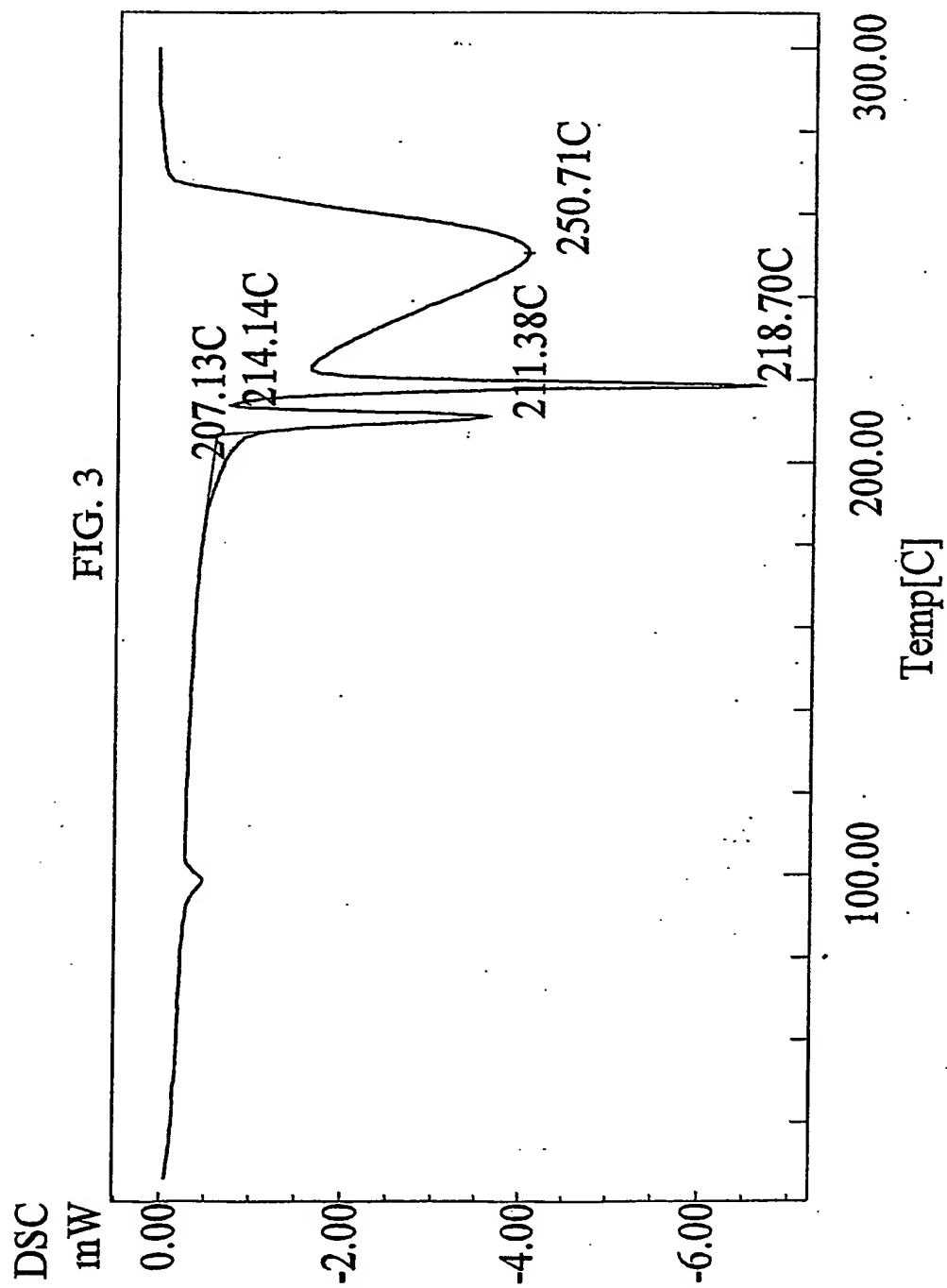
10 16. A method of preventing or treating depression, anxiety, neuropathy comprising administering a novel polymorphic Form 1 or 2 or a mixture of Form 1 and 2 of Venlafaxine of the formula I as defined in claims 1-3 or a pharmaceutical composition as claimed in claims 14 or 15 to a patient in need thereof.

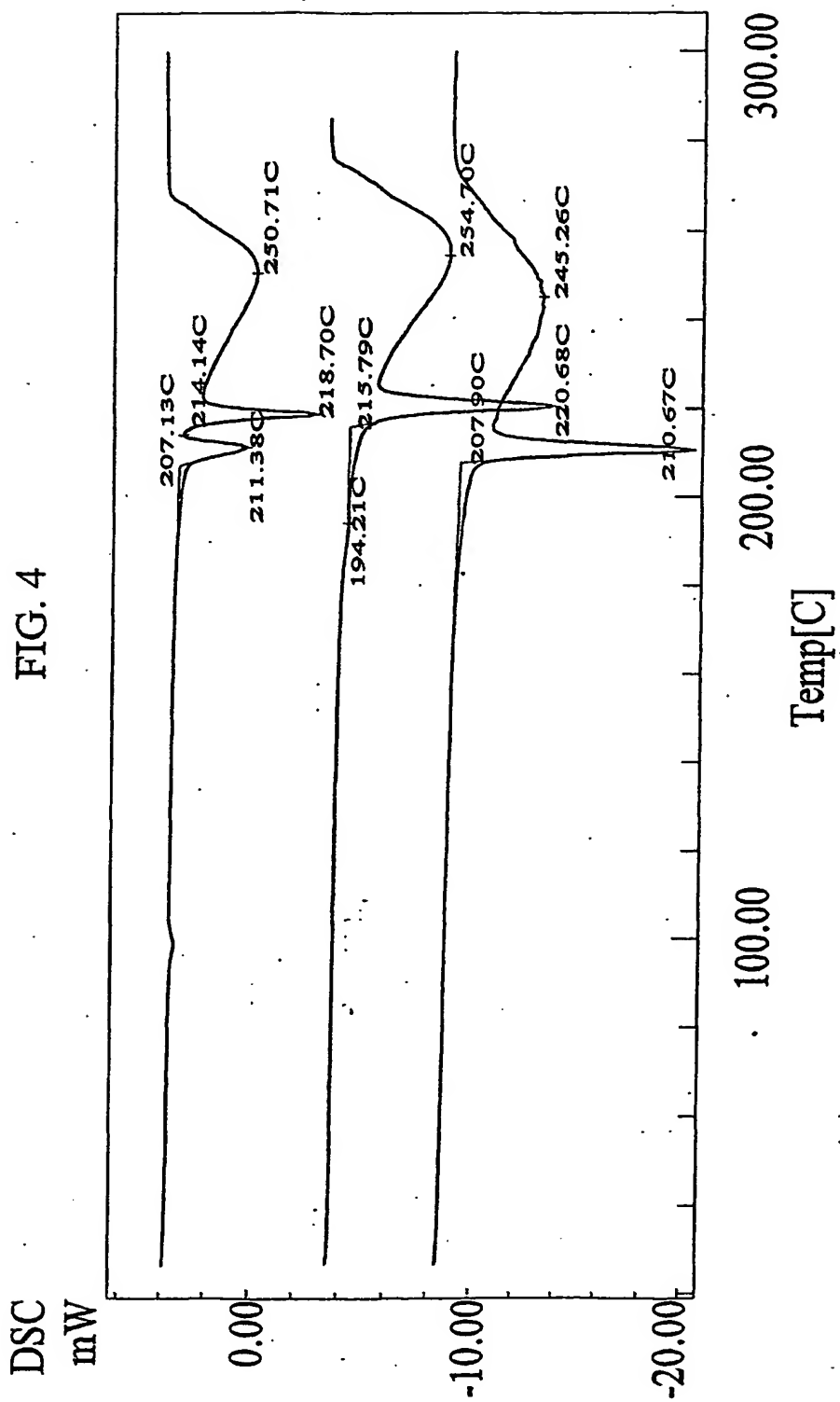
15 17. Use of a polymorphic Form 1 or 2 or a mixture of Form 1 and 2 of Venlafaxine of the formula I as defined in claims 1-3 or a pharmaceutical composition as claimed in claims 14 or 15 for preventing or treating depression, anxiety, neuropathy.

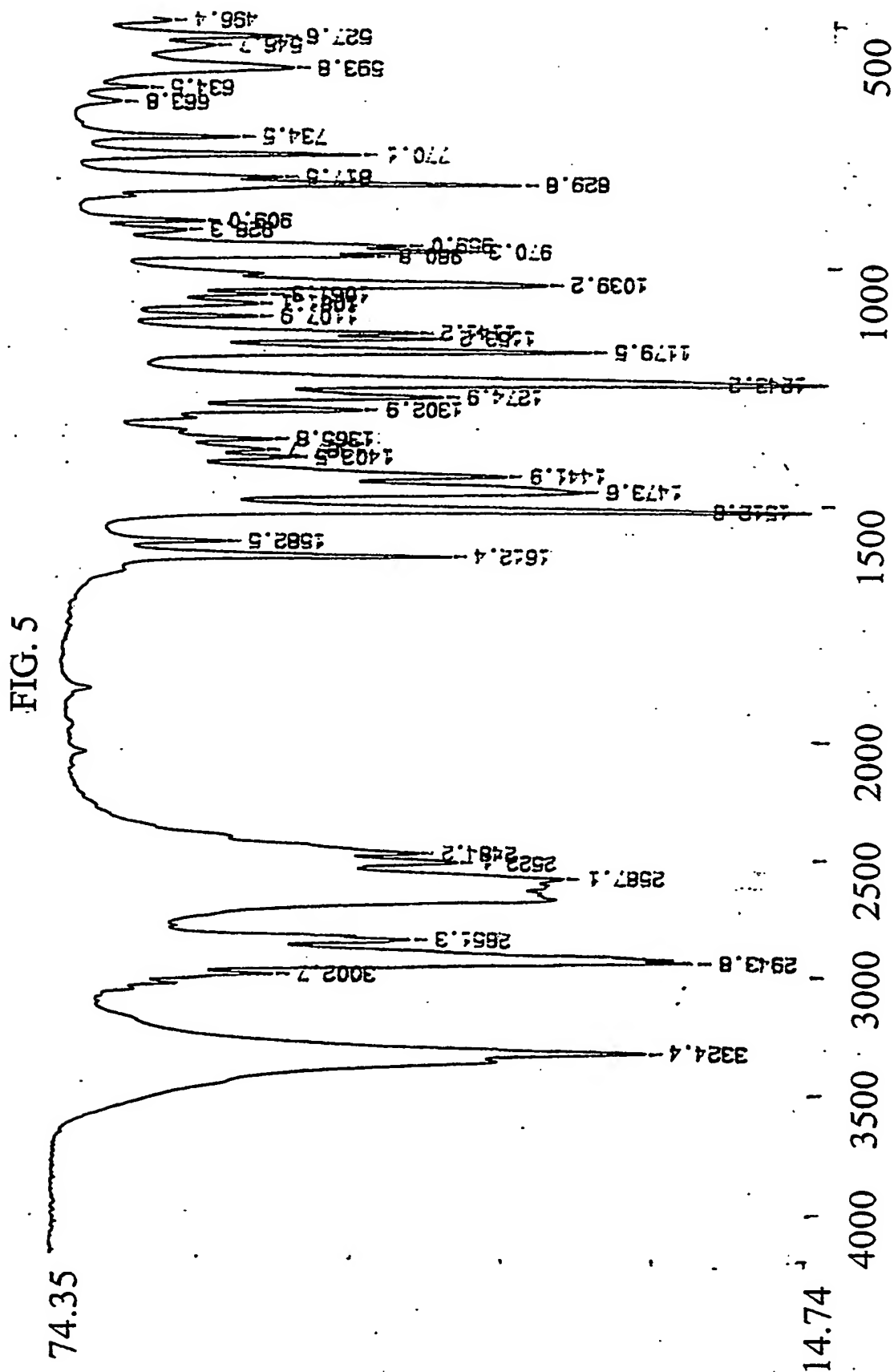
20 18. A medicine for preventing or treating depression, anxiety, neuropathy comprising administering an effective amount a novel polymorphic Form 1 or 2 or a mixture of Form 1 and 2 of Venlafaxine of the formula I as defined in claims 1-3 or a pharmaceutical composition as claimed in claims 14 or 15 to a patient in need thereof.

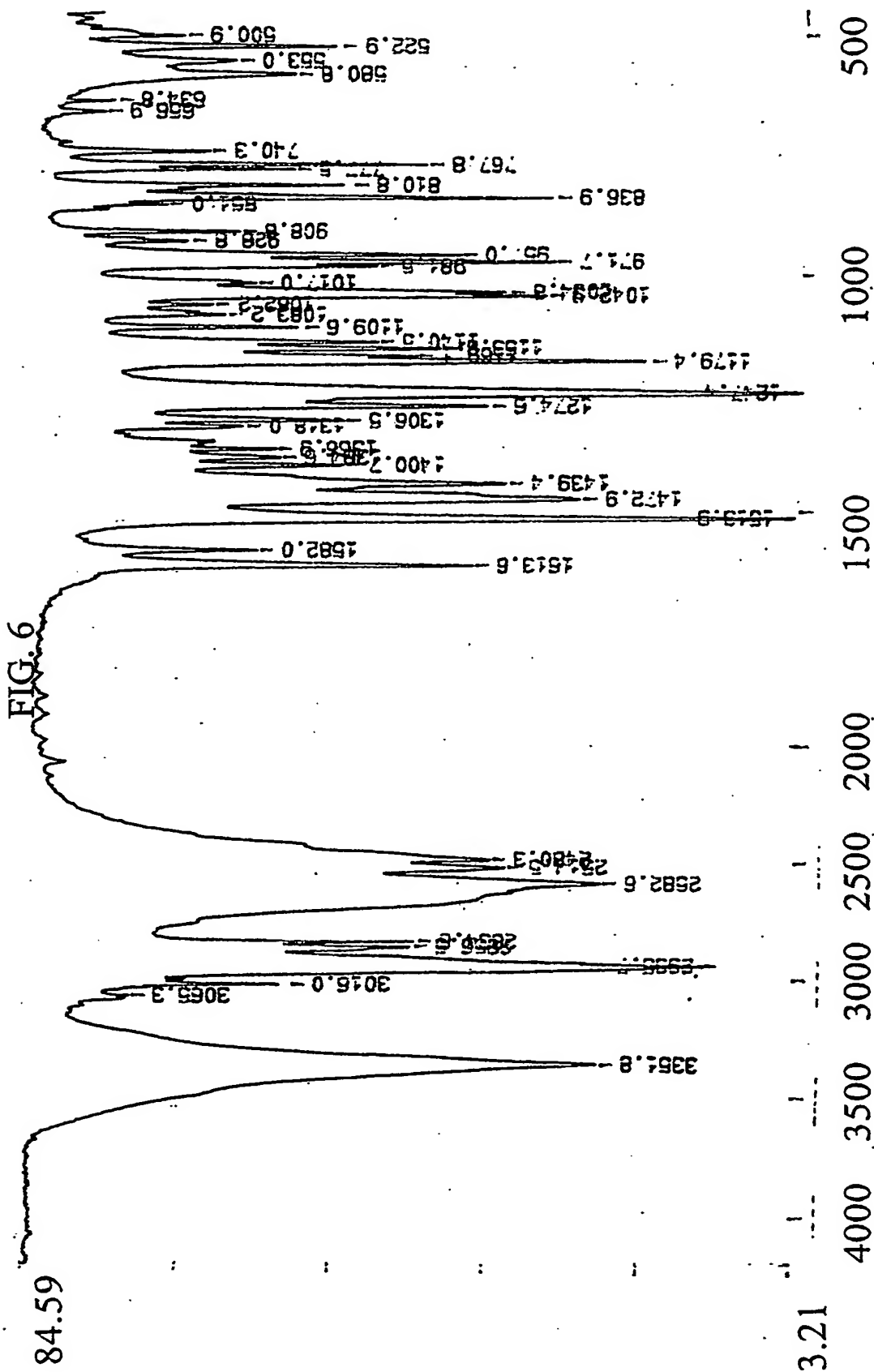












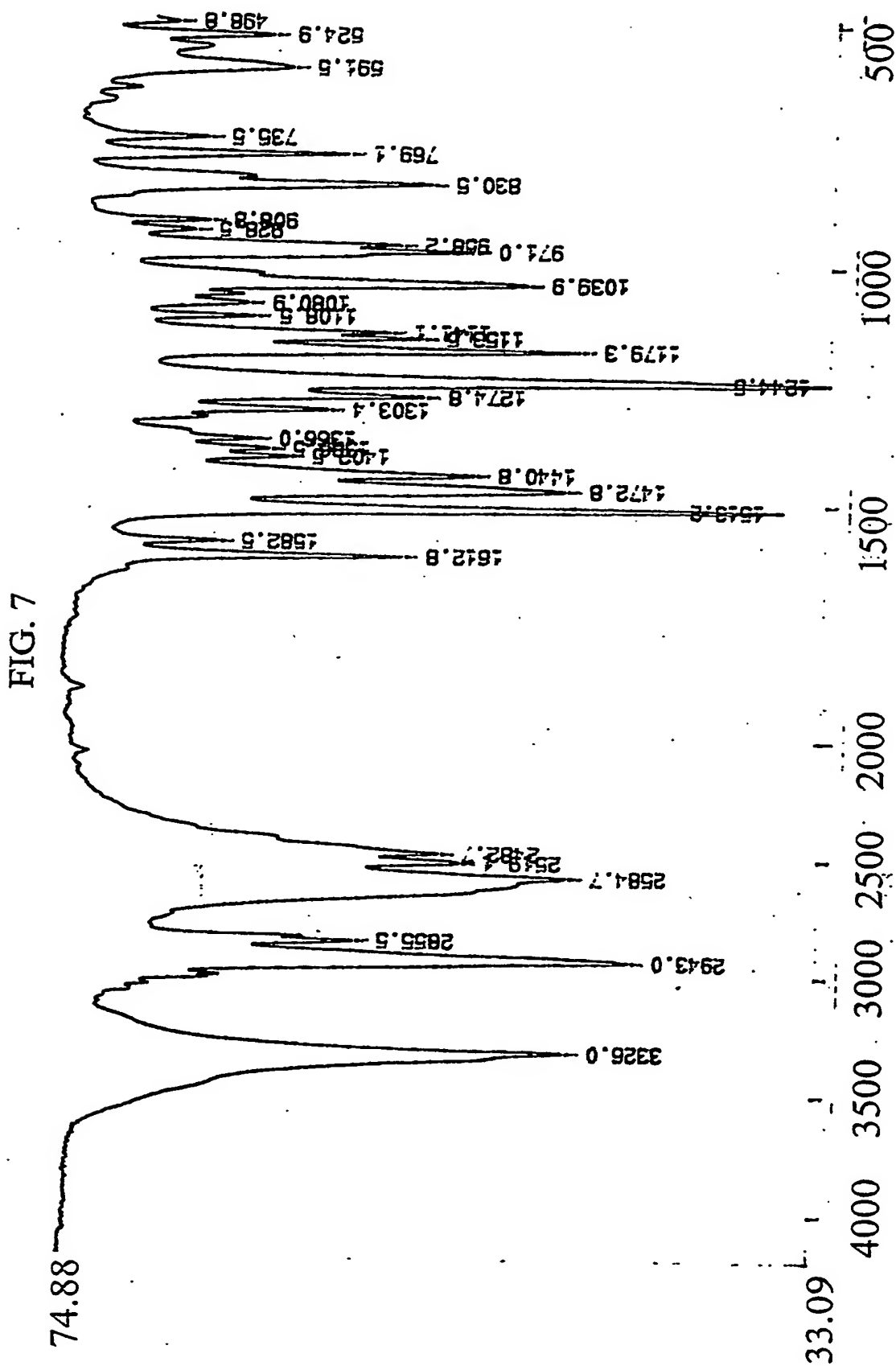


FIG. 8

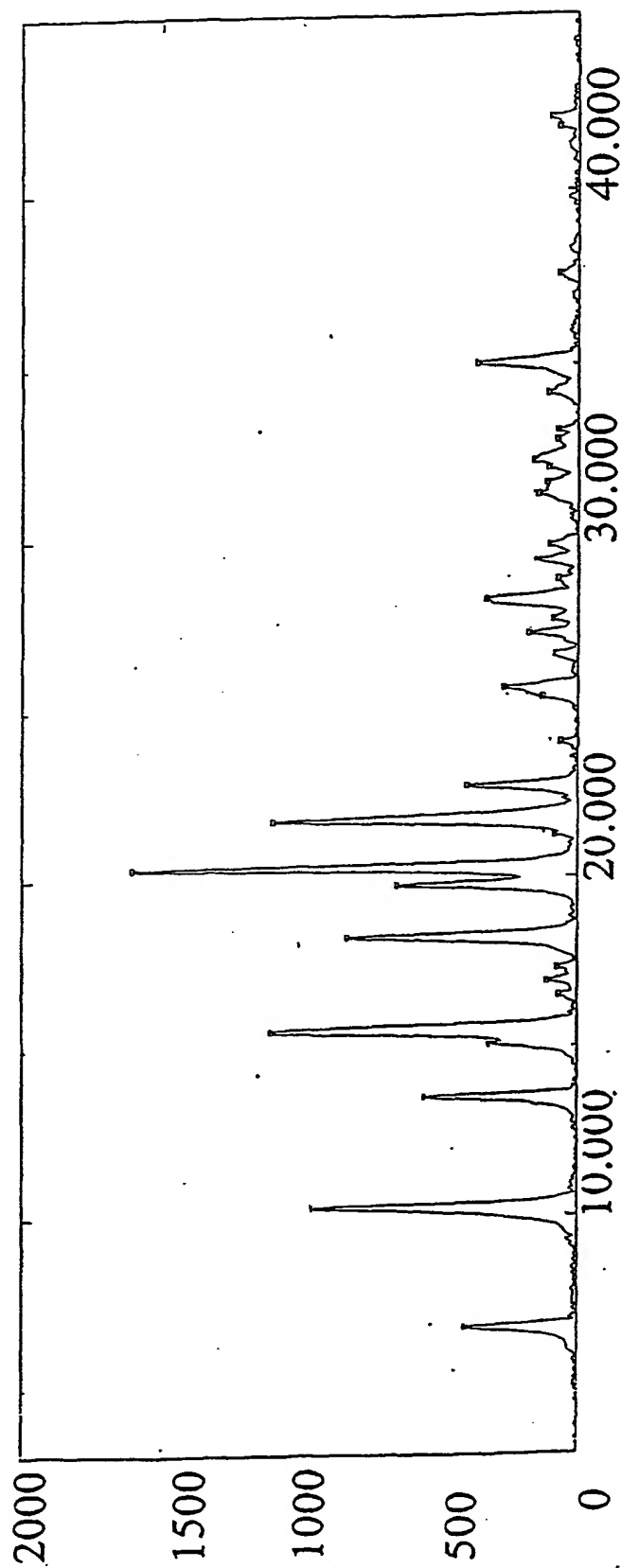


FIG. 9

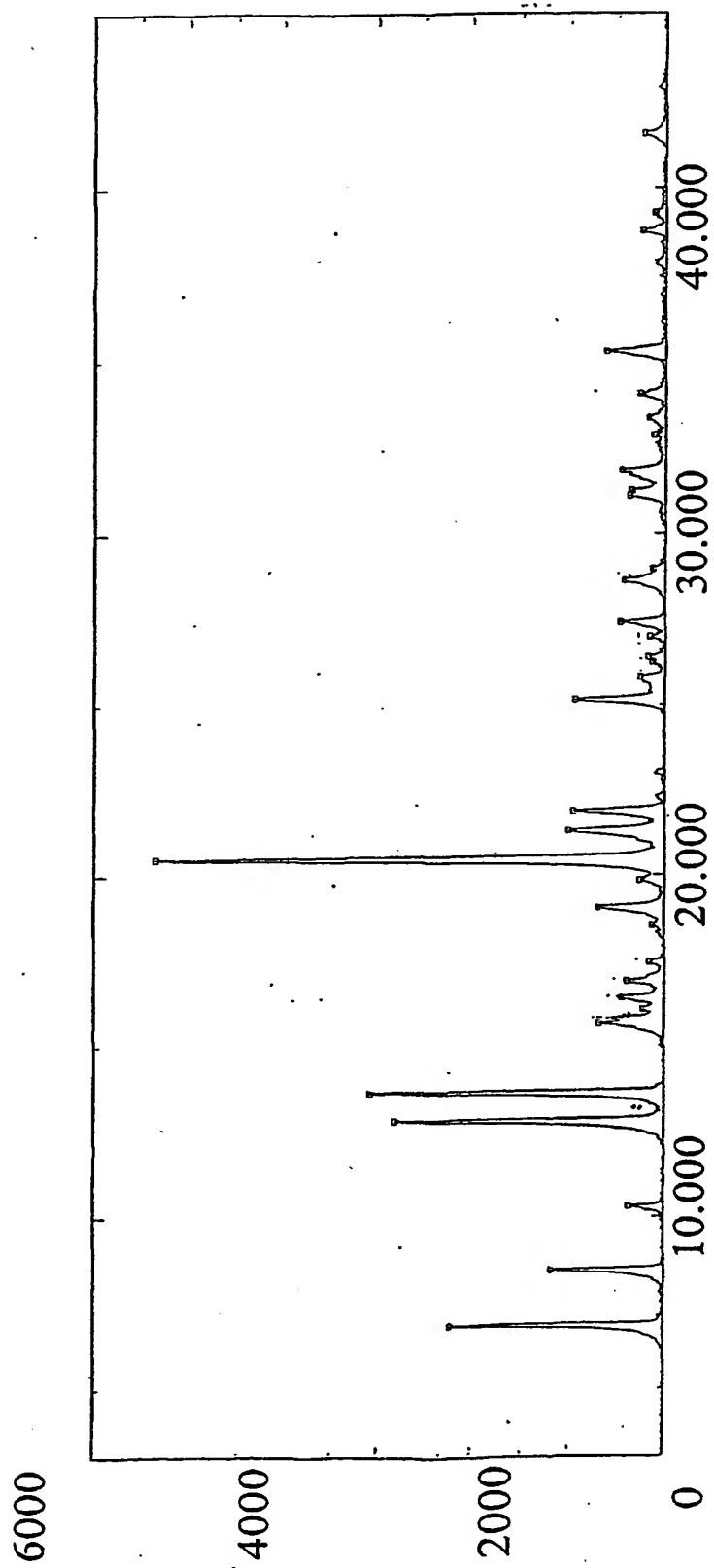


FIG. 10

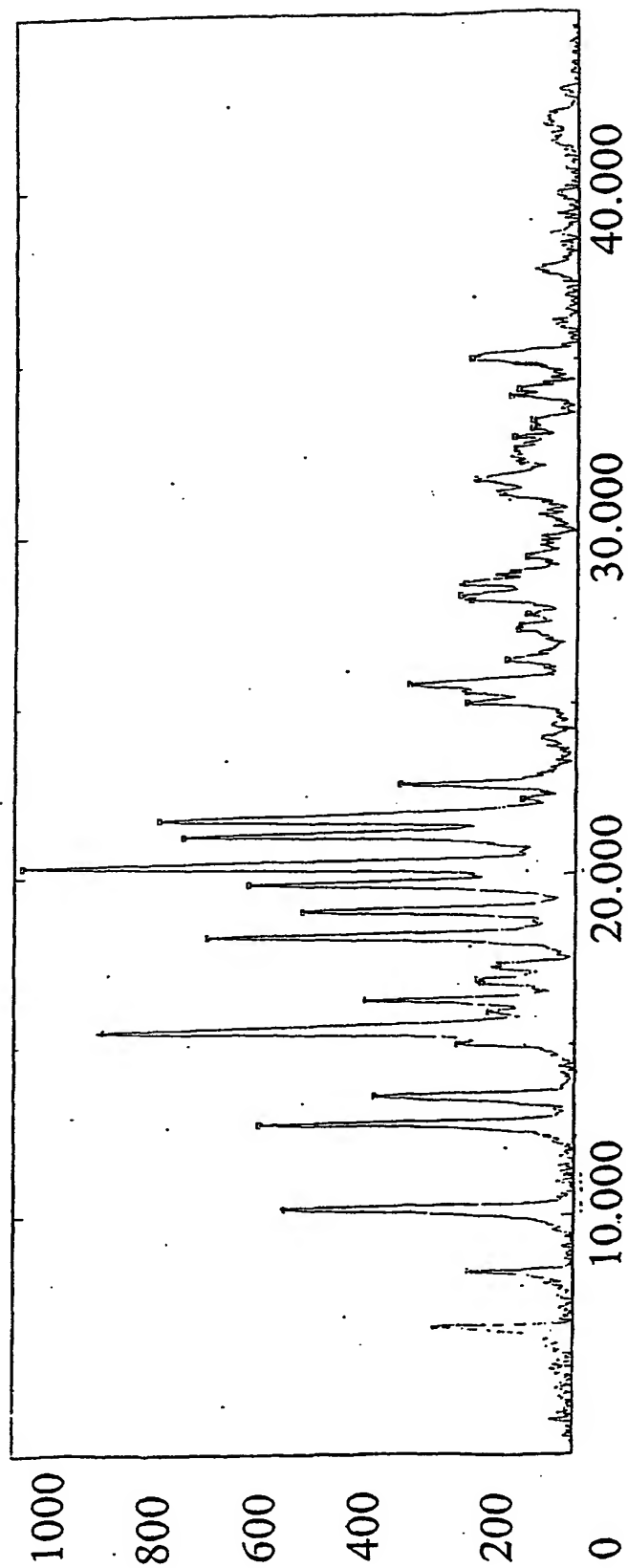
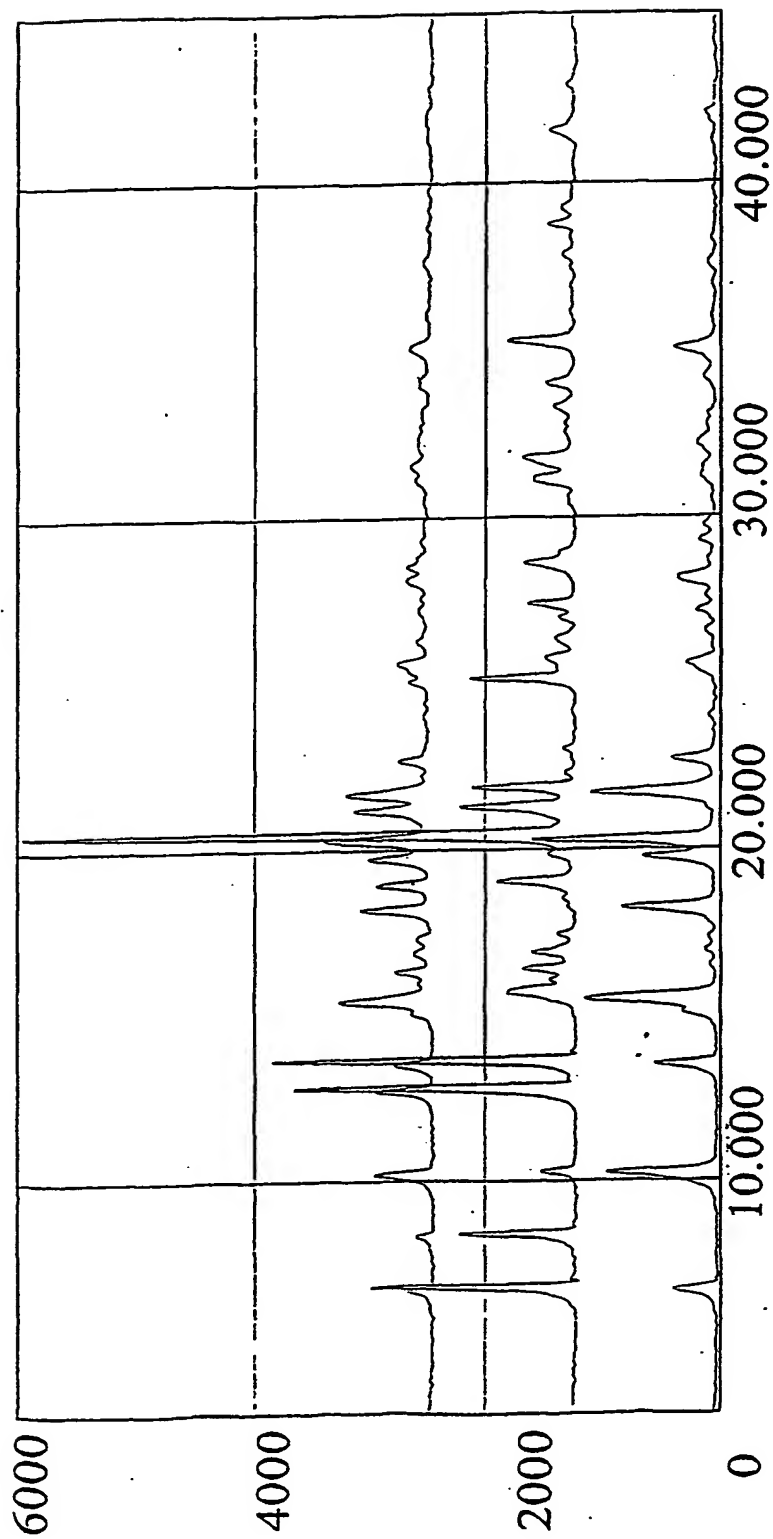
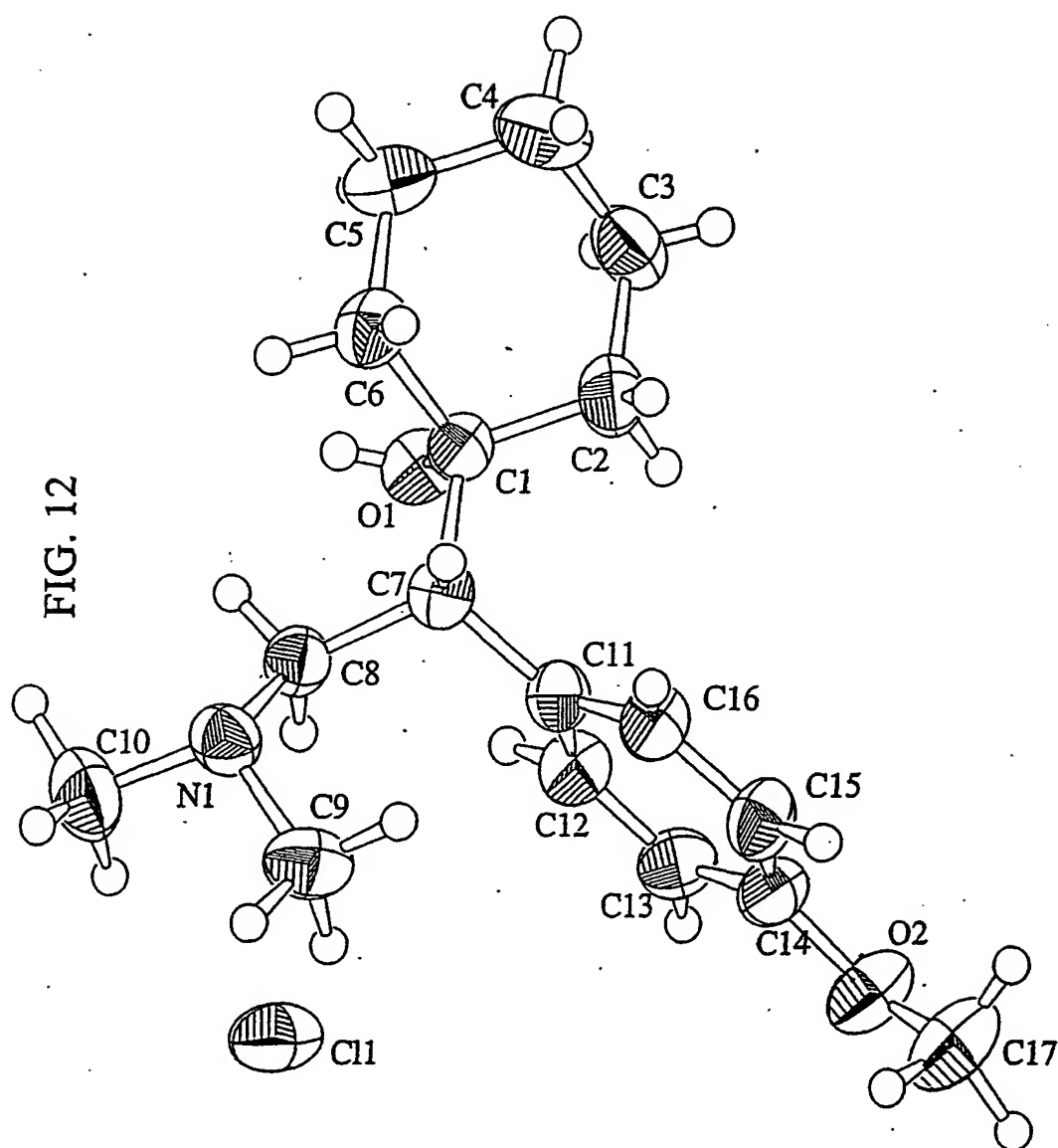


FIG. 11





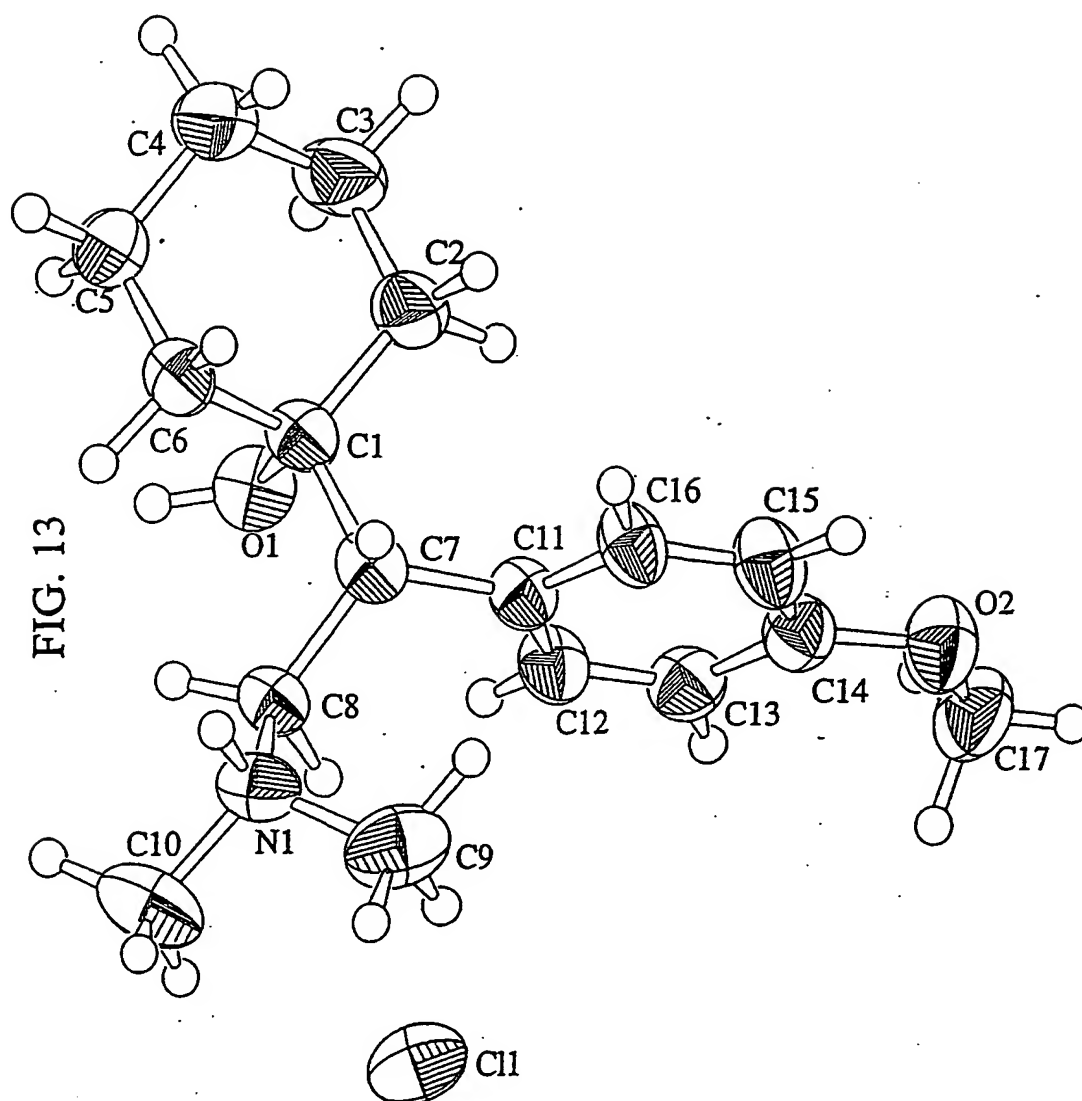


FIG. 14

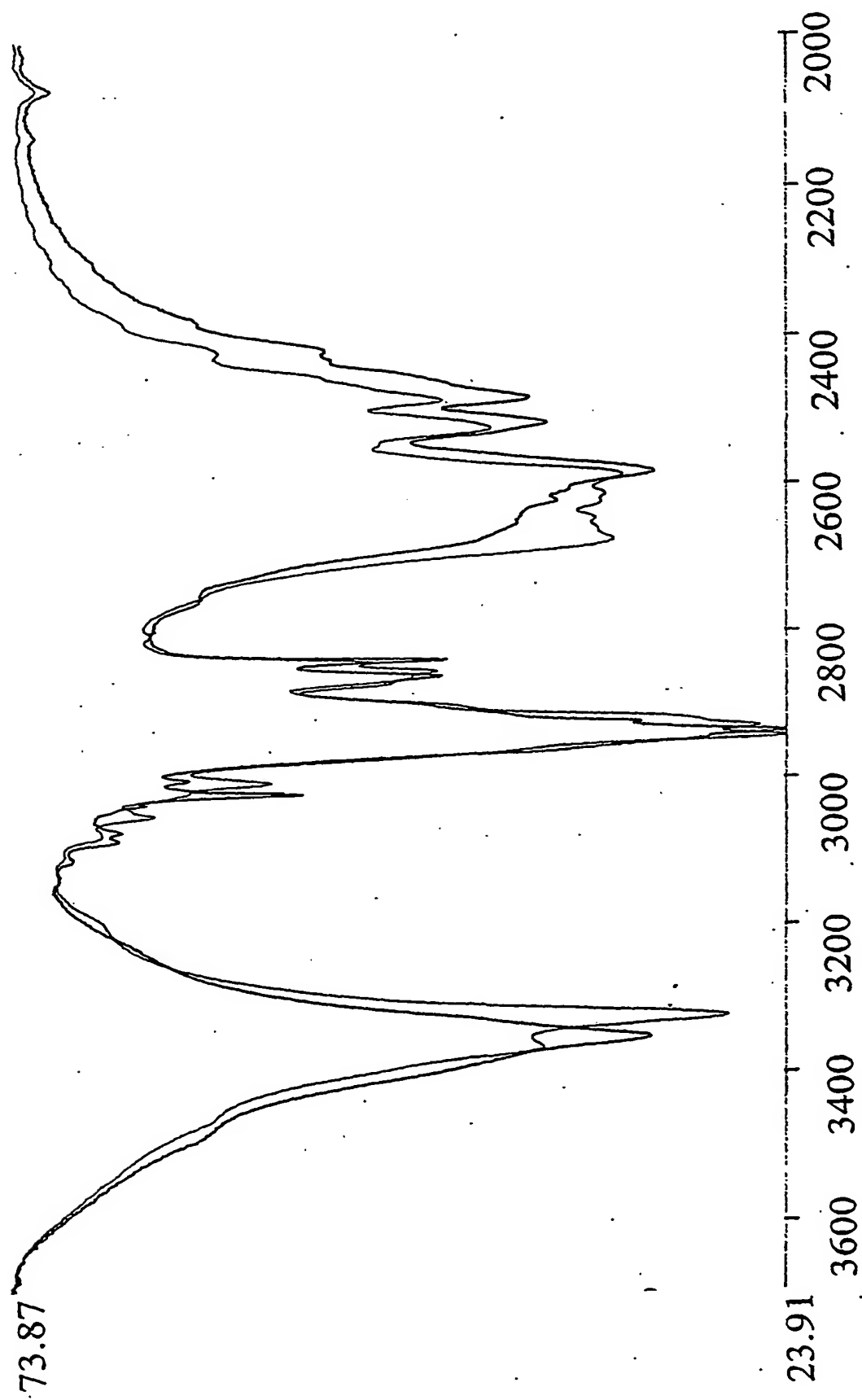


FIG. 15

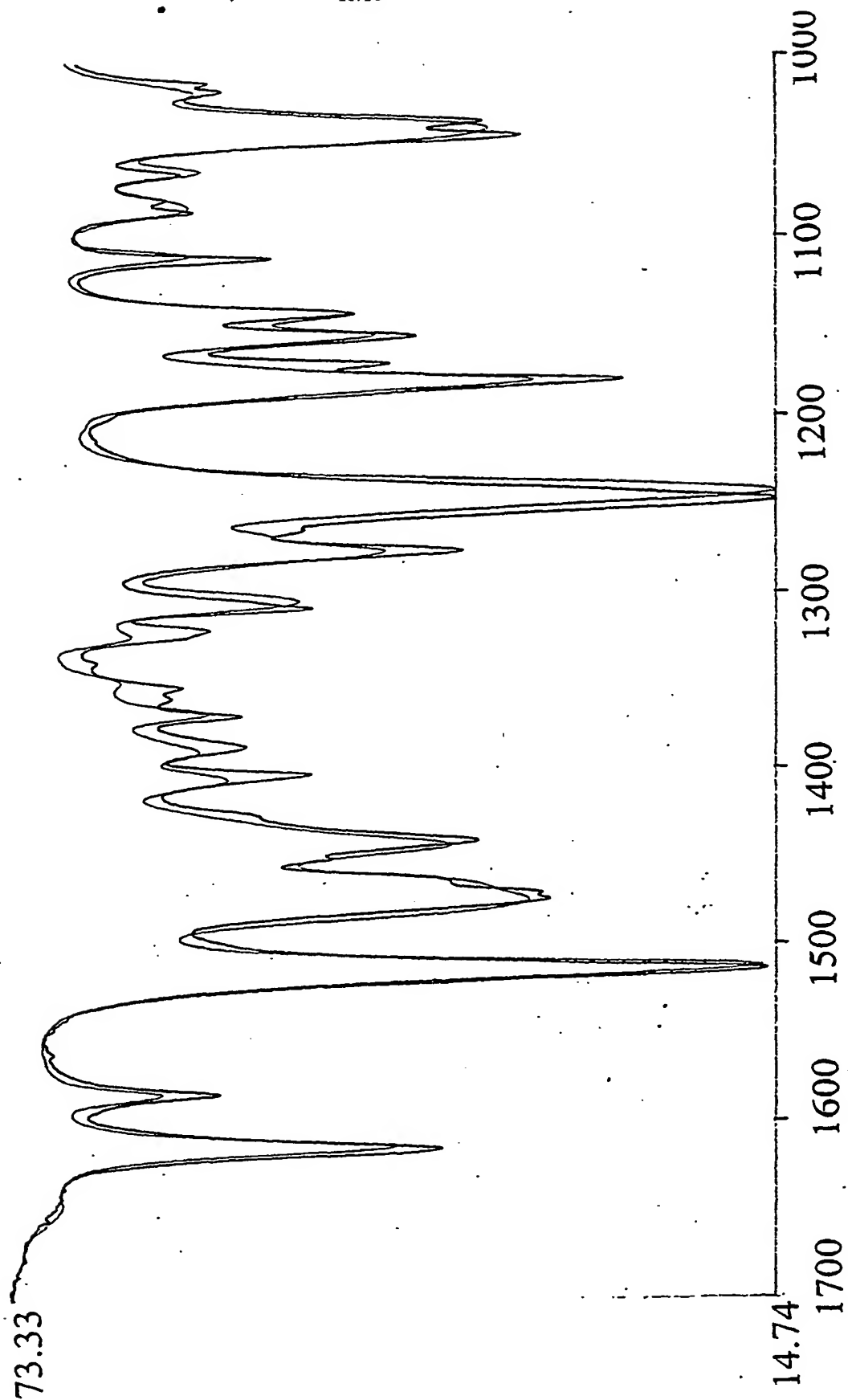


FIG. 16

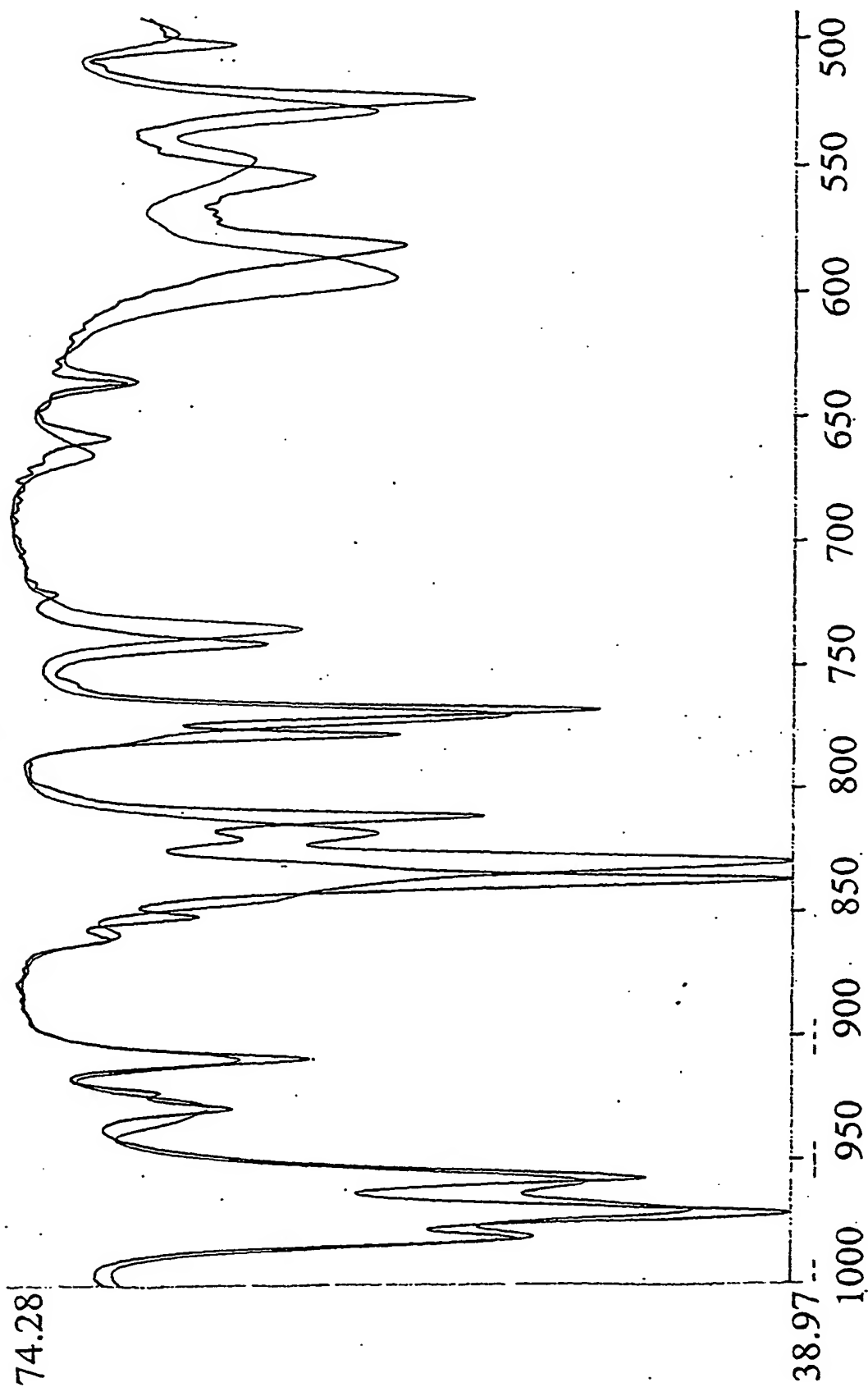
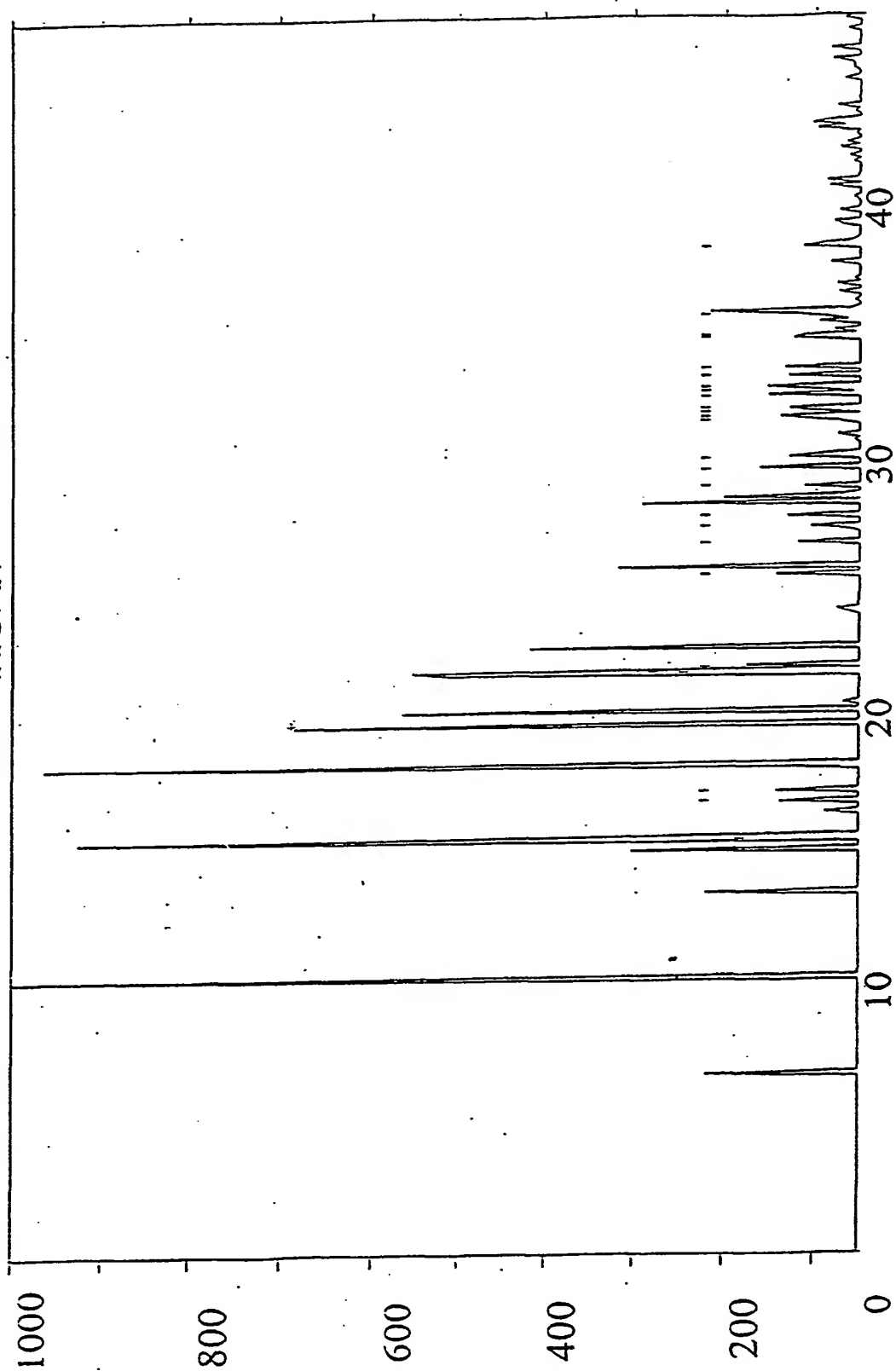
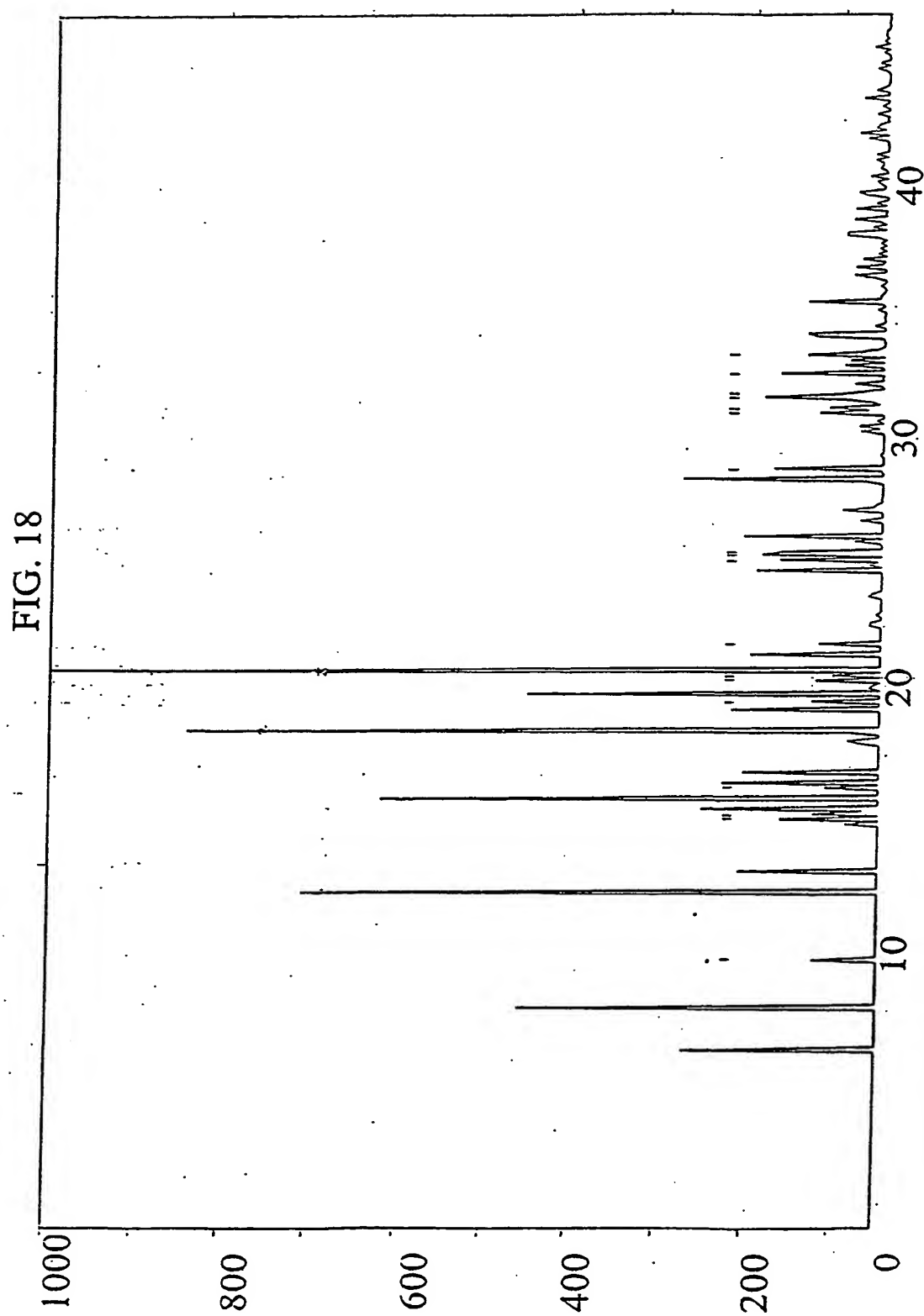


FIG. 17





INTERNATIONAL SEARCH REPORT

national Application No

PCT/IN 00/00121

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C217/74 C07C213/10 A61K31/137 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

BEILSTEIN Data, CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 112 669 A (AMERICAN HOME PROD) 4 July 1984 (1984-07-04) page 20, paragraph 1 claims	1-3, 14-18



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

14 August 2001

Date of mailing of the international search report

22/08/2001

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Pauwels, G

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Information on patent family members

International Application No

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